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MONOCYTIC LEUKEMIA

REPORT OF SIX CASES AND REVIEW OF ONE HUNDRED AND TWENTY-SEVEN CASES

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Since 1913, when the first case of monocytic leukemia was reported by Reschad and Schilling-Torgau, more than one hundred cases have been described. The majority of these reports have appeared since the publication of the excellent reviews of Dameshek and Clough. It is the purpose in this paper to summarize the essential data from the literature, to report 6 more cases and to discuss the origin of the monocyte as deduced from a study of blood smears in 32 cases [1] and of the sternal marrow in 4 of these.

REPORT OF CASES

CASE 1.—A. S., a school girl 7 years of age, was first seen on Jan. 30, 1934, complaining of swelling of the jaw and an itching rash. She was well until January 17, when a painless swelling of the gums and left submaxillary region and an itching rash were noted. A dentist was consulted, and he found no cause for the swelling of the gums. The patient had been exposed to scabies in school. Dr. Ray W. Oldenburg, of Klamath Falls, Ore., was consulted on January 21. He found generalized enlargement of the lymph nodes and a leukocyte cell count of 5,000, with some cells which were difficult to classify. From the blood smear sent to me a tentative diagnosis of monocytic leukemia was made. Dr. Oldenburg [2] referred the patient to me, and I first saw her on January 30. Petechiae were noted on the legs on January 23, and the swelling of the gums and submaxillary nodes had increased. Hemorrhage from the gums occurred on January 29. The child felt well except for itching of the skin.

The significant physical findings were marked swelling of the gums, a small infected area covered by a whitish membrane opposite the lower left first molar, cutaneous lesions, generalized lymphadenopathy and splenomegaly. The cutaneous lesions were of two types, one group being typical of scabies and the other constituting a petechial rash over the upper portion of the chest. The submaxillary,

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1. These 32 smears included those from the 6 cases here reported, 22 demonstrated by Dr. Roy R. Kracke in the scientific exhibit of the American Medical Association at Milwaukee in 1933, 1 sent to me by Dr. A. G. Foord, of Pasadena, Calif., and 3 given to me by Dr. Frank Heck, of the Mayo Clinic.

2. Dr. Oldenburg has given me permission to report this case.

cervical, axillary, epitrochlear and inguinal nodes showed two or three plus enlargement, and the left submaxillary node showed four plus enlargement. All the enlarged nodes were discrete, firm, painless and freely movable. Kramer's dulness and D'Espine's sign were present, indicating enlargement of the posterosuperior mediastinal nodes. The spleen was just at the costal margin and was somewhat firm and not tender. The enlargement of the mediastinal nodes was confirmed by fluoroscopy and a roentgenogram of the chest. The results of the studies of the blood are shown in table 1. The white cell count varied from 1,000 to 7,300, with from 1 to 7 per cent monocytes, from 1 to 20 per cent promonocytes and from 2.4 to 9 per cent monoblasts. The sternal marrow obtained on January 31 consisted almost entirely of monoblasts, with a few promonocytes (fig. 1). The monocytes, promonocytes and monoblasts showed a negative peroxidase reaction. A diagnosis of acute subleukemic monocytic leukemia and scabies was made.

TABLE 1.—*Hematologic Studies*

Case	Date	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	White Blood Cells per Cu. Mm.	Monocytes, Percentage	Promonocytes, Percentage	Monoblasts, Percentage
1	1/31/34	11.22	4.07	5,050	1.6	...	2.4
	2/ 2/34	10.91	4.01	5,450	7.0	...	...
	2/ 3/34	11.59	4.02	3,250	6.0	...	...
	2/ 5/34	10.29	4.11	3,750	6.0	1.0	...
	2/ 6/34	10.55	3.80	5,750	7.0	...	...
	2/ 7/34	9.70	3.28	5,050	7.0	2.0	4.0
	2/ 8/34	8.82	3.72	7,300	...	...	5.0
	2/ 9/34	9.00	3.58	5,500	2.0	1.0	6.0
	2/10/34	10.48	3.56	4,450	1.0	15.0	9.0
	2/12/34	11.73	3.99	2,450	...	20.0	5.0
	2/13/34	11.59	4.07	2,750	2.0	16.0	6.0
	2/14/34	9.29	3.18	1,000	...	8.9	3.5
2	.....	6.21	2.00	3,450	....	....	....
		5.24	1.78	4,425	60.0	....	....
	2/ 6/35	4.14	2.00	8,250	48.0	....	....
	2/ 9/35	....	....	.....	42.0	34.0	13.0
	2/ 9/35*	....	....	.....	....	....	73.0
	2/15/36	....	....	20,350	....	....	....
3	2/21/35	7.65	2.40	54,000	....	....	....
	2/23/35	6.69	1.92	38,650	60.0	1.0	1.0
4	8/16/35*	....	....	.....	5.0	26.5	1.5
	8/24/35	8.56	2.94	27,100	44.0	....	...
5	.....	10.21	3.64	151,000	....	65.0	4.0
6	4/21/36	11.04	3.36	21,300	40.0	....	...
	4/29/36	8.56	2.65	25,750	29.0	....	...
	5/ 1/36	....	....	34,450	15.0	8.0	5.0
	5/ 5/36	8.97	3.14	22,950	32.0	7.0	Occasional

* Sternal marrow was studied.

The patient was admitted to the Doernbecher Memorial Hospital for Children on February 2. The scabies responded quickly to treatment. Sodium perborate paste was applied to the gums after every meal, and a mouth wash of hydrogen peroxide was used every half hour while the patient was awake, in an attempt to prevent Vincent's stomatitis, which occurs as a rule in these cases. Three roentgenographic treatments of about one twentieth of an erythema dose were given over the gums and the anterior portion of the chest on February 2, 7 and 12, and two treatments were given to the spleen, spine and dorsal portion of the thorax. Two transfusions of 250 cc. each were given on February 9 and 11. Infection of the gums was controlled, and the enlargement of the nodes decreased slightly. No discomfort was noted by the patient until February 15, when nausea and vomiting developed. She then complained of a generalized aching pain over the body, especially in the lumbar region, which was controlled by codeine. The tempera-

ture was above normal for the first time on February 4 and rose steadily, reaching 106.6 F. on the evening of February 14. The gums became swollen to such an extent that they extended well above the surface of the teeth. They were entirely free from infection. The patient died at 12:20 a. m. on February 16.

Necropsy.—Gross examination showed petechiae and ecchymoses in the skin. The gums were so swollen that they hid the teeth from view, yet there was no ulceration or bleeding. Generalized enlargement of the lymph nodes and spleen (120 Gm.), multiple hemorrhages in the various serous membranes and hyperplasia of the bone marrow in both the flat and the long bones were noted.

Microscopic examination revealed leukemic infiltration of the lymph nodes, spleen, lungs and liver and surrounding infarcts in both kidneys. Such infiltration was evident also in the appendix, in Peyer's patches of the ileum, in the marrow of both flat and long bones and in the gums. The leukemic infiltrations consisted of monocytes, promonocytes and monoblasts, with a few plasma cells. Many of the promonocytes showed phagocytosed red blood corpuscles. The epithelium of the gums was intact and showed no indications of either necrosis or

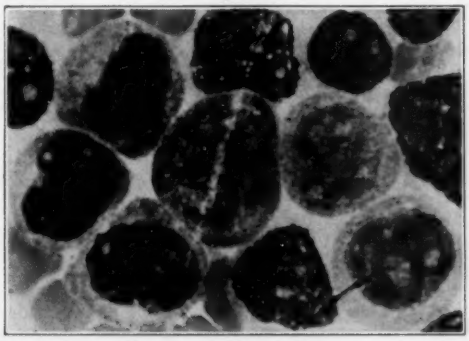

Fig. 1 (case 1).—Photomicrograph (× 1,200) of sternal marrow. One monocyte, two promonocytes and three monoblasts are shown.

infection, the swelling being entirely due to the leukemic infiltration. No transition between lymphocytes and monocytes was observed in the lymph nodes. In both the spleen and the lymph nodes the monocytes had almost crowded out the other types of cells. In the liver the infiltration was confined, as in lymphatic leukemia, to the region of the portal trinities. The marrow from the rib and the middle third of the tibia showed almost complete replacement by monoblasts and highly phagocytic promonocytes. Reticulum cells in the marrow and spleen showed no evidence of hyperplasia.

Case 2.—A woman 36 years of age consulted Dr. C. E. Watts,[3] of Seattle, on Feb. 1, 1935, complaining of a cutaneous rash and nosebleed. She had not felt well since August 1934 and had noticed a cutaneous rash, which had been diagnosed by a dermatologist as erythema multiforme. She had also received treatment for endocervicitis. Physical examination revealed an unusual maculopapular eruption on the face, neck, hands and feet, including the palms and soles,

3. Dr. Watts supplied the report of the history and physical examination and gave me permission to report this case.

and petechiae on the thighs (fig. 2). She had a profuse nosebleed. The submaxillary and axillary nodes showed one plus enlargement. The spleen was not palpable but was enlarged to percussion. The white cell count was 3,450, with many immature cells. The red cell count was 2,000,000, with a normal color index.

On the basis of a blood smear sent to me for examination, a tentative diagnosis of acute monocytic leukemia was made. Examination of sternal marrow, obtained on February 15 and sent to me by Dr. Watts, showed a nucleated cell count of 170,000 per cubic millimeter, with nearly all the cells monoblasts or promonocytes, thus confirming the diagnosis of monocytic leukemia. The patient had a temperature of 100 to 101 F., and swelling and ulceration of the pillars of the

Fig. 2 (case 2).—The cutaneous lesions in monocytic leukemia.

fauces developed, but there was only slight swelling of the gums. The cervical lymph nodes became considerably enlarged. The data for the blood are given in table 1. Death occurred on February 17.

Necropsy, by Dr. A. Balle, of Seattle, revealed multiple hemorrhages in the skin, lungs, heart, liver and spleen, with leukemic infiltration of these organs, with generalized enlargement of the lymph nodes, with the liver extending 5 cm. below the costal margin and with the spleen approximately three times the normal size. A bicornuate uterus and double vagina were noted. The pathologist stated that because many of the cells showed a positive reaction for peroxidase he felt that this was a case of acute myelogenous leukemia, but the blood smears and preparations of the sternal marrow which I examined showed clearly that the immature cells belonged to the monocyte series.

CASE 3.—R. L., a man aged 62, entered the Multnomah County Hospital on Feb. 20, 1935, complaining of "boils." He had been well until the spring of 1933, when the first boil developed on the chest. Since that time he had had numerous boils scattered over the body. At the time of his admission to the hospital there was a large carbuncle on the back of his neck. Since December 1934 he had noticed frequent epistaxis and increased weakness. The lesion on the back of the neck began to develop on Feb. 1, 1935.

Physical examination showed that the temperature ranged from 96 to 100 F. and that the pulse rate ranged from 72 to 112. The respiratory rate was 20, and the blood pressure was 100 systolic and 70 diastolic. There was a large carbuncle on the back of the neck. No swelling of the gums, petechiae or enlargement of the lymph nodes was noted. The spleen and liver were slightly enlarged to percussion. The white cell count varied from 38,650 to 54,000, with 60 per cent mature monocytes. The hemoglobin value ranged from 6.69 to 7.65 Gm., and the red cell count ranged from 1,920,000 to 2,940,000. The details of the studies of the blood are shown in table 1. A diagnosis of chronic monocytic leukemia with myelophthisic anemia and carbuncle of the neck was made. The patient died on February 28.

Necropsy revealed, in addition to the carbuncle and furunculosis, enlargement of the spleen (425 Gm.) and liver (2,250 Gm.), petechiae in the pericardium and leukemic infiltration, consisting chiefly of mature monocytes in the kidneys, spleen, lymph nodes and marrow. The infiltration in the liver was chiefly in the periportal areas. There was terminal bronchopneumonia.

CASE 4.—H. R. R., an Italian aged 64 years, entered St. Vincent's Hospital on July 30, 1935, under the care of Dr. Roy C. McDaniels.[4] He complained of loss of weight and fatigue. He had been well until January 1934, when he noticed general malaise, with increasing fatigability and loss of weight. The total loss of weight was 35 pounds (16 Kg.).

Physical examination revealed generalized pallor of the skin and mucous membranes and a two plus enlargement of the spleen, but no petechiae, no swelling of the gums and no enlargement of the lymph nodes or liver. The white cell count was 27,100, with 44 per cent monocytes. The sternal marrow on August 16 showed 5 per cent monocytes, 24 per cent promonocytes, 2.5 per cent promonocytes in mitosis and 1.5 per cent monoblasts.

A diagnosis of monocytic leukemia was made by Dr. T. D. Robertson, pathologist for St. Vincent's Hospital, and I confirmed this diagnosis when I saw the patient in consultation. Details of the studies of the blood are shown in table 1. The patient was discharged from the hospital on August 29, feeling somewhat improved. After that he felt better and gained some weight, but a year later he was emaciated, weak and anemic, and, according to Dr. Robertson, so many monocytes and promonocytes were present in the blood that there was no question as to the correctness of the diagnosis. He died about March 13, 1937.

CASE 5.—Mrs. J. D., a woman aged 76, was first seen on Oct. 18, 1935, by Dr. Laurence Selling,[5] of Portland, Ore. She complained of weakness and a "cold" and showed nothing significant on physical examination except hyperemia of the pharynx. On October 23 the temperature was 99.2 F., and redness of the pharynx was still present. The patient was seen daily thereafter by Dr. Selling

4. Drs. Roy C. McDaniels and Thomas D. Robertson, of Portland, Ore., gave me permission to include a report of this case. A full report will be given by them in a separate paper.

5. Dr. Selling gave me permission to report this case.

TABLE 2.—*Summary of Cases of Monocytic Leukemia*

Case	Authors	Number	Age	Sex	Swollen Gums	Petechiae	Enlarged Lymph Nodes	Enlarged Spleen	Enlarged Liver	White Blood Cells	Monocytes, %	Promonocytes, %	Monoblasts, %	Peroxidase Reaction	Duration of Illness	Necropsy	Comment
1	Reschad and Schilling-Torgau	..	33	M	+	+	0	+	+	15,100- 56,000	72.0-74.0	....	.....	—	9 wk.	+	Cutaneous lesions
2	Fleischmann.....	..	47	M	+	0	—	—	+	3,700- 36,000	25.0-65.0	....	.....	?	7.5 mo.	+	
3	Bingel.....	..	48	M	+	+	+	+	+	4,500- 16,500	44.0	....	.....	?	9 wk.	+	Biopsy of sternal marrow
4	Rosenthal, 1921.....	1	5	M	+	+	+	+	+	245,000	87.0	....	0.2 ?	—	5 wk.	—	Followed typhus
5		2	..	..	..	..	..	..	..	.....	.....	....	.....	..	.....	..	
6		3	34	M	0	0	0	+	+	660- 3,000	44.0	....	.....	?	4 mo.	+	Not described
7	Komiya and Hayashi	..	20	M	+	+	+	310	1,250	52,800-317,500	30.0-80.0	....	.....	+	5 wk.	+	
8	Ewald, Frehse and Hennig	1	32	M	+	+	0	0	0	140,000	80.0-87.0	....	4.5-8.0	?	24 days	+	Probably acute myelogenous leukemia
9		2	30	M	0	0	0	0	0	99,000	5.0- 7.0	90.0 ?	.....	+	6 wk.	+	Probably acute myelogenous leukemia; lymphoidocytes
10		3	29	F	0	0	0	0	0	56,000	60.0	....	24.0 ?	?	?	+	Probably acute myelogenous leukemia
11	Ewald.....	..	60	M	+	0	0	+	—	15,000	0.2	....	9.5-95.0	+	6 wk.	+	
12	Alder.....	7	30	M	+	0	0	0	0	100,000	40.5 ?	30.0 ?	12.0 ?	?	Few wk.	?	Probable case
13		8	78	M	0	0	0	0	0	8,000- 46,000	36.5 ?	....	24.0 ?	?	3 mo.	?	Probable case
14		12	57	F	+	0	—	—	0	80,000-400,000	70.0 ?	13.5 ?	16.0 ?	+	14 days	?	Probable case
15	Naegeli.....	2	34	M	+	+	+	—	—	7,800-126,000	1.3-27.5	17.6	10.2-90.9	?	2.5 mo.+	+	
16	Hoff.....	4	41	M	+	0	0	390	0	1,600- 2,500	15.0-42.5	....	.....	—	7.5 wk.?	+	
17	Merklen and Wolf.....	..	30	M	+	+	0	+	0	20,500- 43,000	85.0-93.0	....	.....	?	3 mo.	+	
18	Swirtschewskaja.....	..	27	M	—	—	—	+	+	6,400-416,000	1.6- 3.1	....	.....	—	8.5 mo.	+	Probably acute lymphatic leukemia
19	Melerovitch.....	..	19	M	+	0	+	+	+	11,000- 80,000	75.0-89.0	....	.....	?	?	+	
20	Ugriumow.....	..	30	M	0	+	+	+	+	36,000	46.5	....	.....	?	23 days	+	Questionable case
21	Hannema.....	..	11	M	+	+	+	+	+	107,000-120,000	81.0	....	.....	?	19 days	+	
22	Hittmair, 1928.....	..	63	M	+	0	—	+	+	38,200	83.0	....	.....	+	1 mo.	+	
23	Tschistowitsch and Bykowa	..	63	M	0	0	+	500	1,650	6,000- 6,600	1.0- 7.5	....	.....	?	1.5 mo.	+	Acute aleukemic type
24	Weissenbach, Martineau, Raulot-La Pointe, Bourdillon and Ronget	..	52	M	—	+	+	+	0	13,200-198,000	34.0-73.0	....	.....	?	14 mo.	—	Cutaneous lesions; tuberculosis
25	Wyschegorodzewa.....	..	38	F	+	—	—	310	1,610	1,900- 22,700	16.0-83.0	....	1.0-7.0 ?	—	8 mo.	+	Cutaneous lesions; pains in bones; sternal puncture
26	Sega and Brustolon...	..	18	M	+?	+	+	265	2,100	34,740- 40,780	55.4	....	.....	?	2 mo.	+	
27	Muenzer.....	..	8	M	+	+?	+	+	+	8,000- 52,000	3.0-82.0	....	.....	—	3 wk.	—	Cutaneous lesions
28	Farley.....	..	62	F	+	—	—	—	—	10,000- 72,000	46.0-95.0	....	.....	+	10 mo.	—	
29	Dias.....	..	6	F	0	0	0	0	0	3,750- 4,030	48.0-55.0	....	.....	?	3 mo.	—	Questionable case
30	Bock and Wiede.....	..	34	M	—	+	+	870	+	10,000- 46,000	54.0-85.0	....	.....	—	22 days	+	Sternal marrow normal
31	Rosenthal, 1930.....	4	0	0	0	0	0	0	0	73,000-146,000	70.0-78.0	....	.....	?	?	?	

32	Dameshek	1	55	M	+	—	+	+	+	19,300-147,000	20.5-78.5	....	.....	+	3 mo.	—	Cutaneous lesions; pains in bones
33		2	70	M	+	—	+ —	—	—	13,300-124,000	19.0-86.8	....	.....	—	10 wk.	—	Biopsy of sternal marrow
34	Hittmair, 1930	..	0	F	+	+	+	+	—	160,000	28.6-55.0	....	.....	+	14 days?	+	
35	Clough	..	62	M	+	+	+	420	2,470	174,000-262,000	87.0	....	0.5	—	?	+	
36	Castellano and Girardet	..	45	F	0	+	—	+	+	79,800- 93,400	18.0-39.0	19.0-25.0	25.0-57.0	?	?	—	
37	Lawrence, Josey and Young	1	0	M	+	+	+	0	+	9,300- 47,500	42.0-86.5	....	.....	+	3 mo.	—	
38		2	61	F	0	0	0	+	+	8,100- 20,000	30.0-51.5	....	.....	+	?	0	Biopsy of sternal marrow; remission after radiation
39		3	13	M	+	+	+	360	1,470	18,800-180,700	66.0-83.0	....	0.0-5.0	+	4 wk.	+	
40	Cooke	..	19	M	+	—	—	+	0	50,000	87.0	....	.....	—	4 wk.	—	
41	Schwarz	..	30	F	+	+	+	600	2,000	13,000-104,000	46.0-89.0	....	0.0-18.0?	+	5 wk.	+	Pains in bones
42	Cuatrecasas and Urtubey	..	0	M	0	0	+	+	+	287,000-366,000	95.0-99.0	....	.....	?	13 mo.	—	
43	Rucks and Cunningham	..	60	F	0	+	—	280	1,920	5,000- 36,000	13.0-51.0	....	0.0-44.5	?	6 mo.	+	Monoblasts included promonocytes
44	Invernizzi	..	27	M	+	+	+	+	0	70,000	85.0	....	2.0	?	5-6 wk.	—	Joint pains; large hematomas; cerebral hemorrhage
45	Asselstine	1	35	M	+	+	+	300	3,240	198,000-380,000	5.0-82.0	....	.....	?	4 mo.	+	
46		2	33	M	+	0	+	+	+	7,400- 12,000	0.0-64.0	....	.....	?	?	?	
47	Böhne and Huismans	..	50	F	—	—	+	1,430	2,370	1,800- 4,200	3.0-27.0	....	.....	—	2.5 yr.	+	
48	Reich	..	33	M	+	0	+	+	0	8,100- 52,300	14.0-69.0	....	0.0-50.0?	?	9 wk.	—	
49	Gardner	..	47	F	+	+	+	375	2,125	17,800-246,600	6.0-80.0	....	0.0-38.0?	?	51 days	+	
50	Fontana	..	43	M	—	—	+	+	+	1,400-250,000	66.0	....	.....	?	4 yr. 5 mo.	?	Biopsy of marrow; probably myelogenous leukemia
51	Sydenstricker and Phinizy	..	47	F	+	+	+	+	+	3,500-168,000	47.0-89.0	0.6-28.9?	0.0-1.2	—	4 mo.	—	
52	Farrar and Cameron	..	55	M	+	+	+	+	+	11,400-210,000	0.0-80.0	0.0-4.3	0.0-86.0?	+	7 mo.	—	
53	Pellegrini	..	68	M	0	—	+	+	+	38,000-105,000	80.0	....	.....	?	3.5 mo.	?	
54	Mesropyan	..	2	F	0	0	—	+	0	44,900- 93,400	64.5-80.0	....	.....	?	?	—	Bilateral exophthalmos
55	Orr	1	40	M	0	0	+	270	2,520	1,800- 10,000	18.0-75.0	....	.....	+	18 mo.?	+	Boils
56		2	71	M	0	0	+	510	1,870	4,400-140,000	56.0-94.0	....	.....	+	3 mo.	+	
57	Dubinskaja and Bakaltschuk	..	53	F	+	+	+	+	+	19,000- 89,000	61.0-78.0	....	1.0-4.0?	—	8 mo.	—	Pains in bones
58	Andréoli and Fourest	..	8	M	0	+	+	+	0	28,700- 42,500	79.0-89.0	....	.....	?	8 wk.	?	
59	Cisl	..	9	F	+	+	+	+	+	318,000-384,000	4.0- 5.0	32.0-33.0	12.0	?	10 days?	—	Necrotic angina
60	Lucherini	..	77	M	+	+	0	+	+	40,000- 65,000	81.0	....	.....	?	23 days	+	Cutaneous lesions
61	Fowler	1	64	M	+	—	+	170	0	40,500-285,000	13.0-48.0	....	.....	?	3 mo.?	+	
62		2	43	M	+	—	+	550	2,900	49,000-118,000	72.0-84.0	....	.....	—	5.5 mo.	+	Cutaneous lesions
63		3	44	M	+	—	+	+ —	+	10,250- 40,000	23.0-88.0	....	.....	+	9 wk.	—	
64	Bykowa	1	24	M	+	+	+	145	+	5,600- 10,000	78.0-83.0	....	4.5	+	6 wk.	+	Cutaneous lesions; abdominal pain with diarrhea
65		2	24	M	0	0	+	+	—	4,600	84.0	....	.....	?	9 wk.	+	Biopsy
66	Grenet, Levent and Isaac-Georges	1	3	F	0	+	+	+	+	70,000-157,400	6.0	....	82.0-83.0?	?	?	—	
67		2	10	M	+	+	+	—	—	2,200- 65,300	3.0-33.0	....	25.0-91.0	?	3 mo.	— +	
68		3	2½	M	0	+	+	+	+	20,700- 22,800	10.5-46.0	0.6	73.0	?	?	—	
69	Tidswell	..	12	M	—	0	+	+	+	1,000- 10,000	42.0	....	.....	?	4 mo.	+	

TABLE 2.—*Summary of Cases of Monocytic Leukemia—Continued*

Case	Authors	Number	Age	Sex	Swollen Gums	Petechiae	Enlarged Lymph Nodes	Enlarged Spleen	Enlarged Liver	White Blood Cells	Monocytes, %	Promonocytes, %	Monoblasts, %	Reaction for Peroxidase	Duration of Illness	Necropsy	Comment
70	Foord, Parsons and Butt	1	17	M	+	+	+	+	2,400	25,100- 60,000	63.0-91.0	....	.....	—	7 wk.	+	
71		2	22	F	+	—	+	550	2,100	1,600- 37,450	1.0-94.0	....	.....	—	3 mo.	+	
72		3	58	F	+	—	+	—	0	35,400- 76,000	64.0-72.0	....	9.0?	?	11 wk.	—	Biopsy of lymph node
73		4	52	F	+	—	—	—	—	92,700-116,800	85.0-88.0	....	1.0?	—	4.5 wk.	—	
74	Marchal, Bargeton and Mahoudeau	1	41 to 60	M	0	0	+	+	..	4 cases-	.....	....	.....	?	?	?	Two cases of persistent
75		2		M	0	0	+	+	..	80,000-334,000	.....	....	.....	?	?	?	diarrhea
76		3		M	0	0	+	+	..	.....	.....	....	.....	?	?	?	
77		4		M	0	0	+	+	..	.....	.....	....	.....	?	?	?	
78		5		M	0	0	+	+	..	4 cases-	.....	....	.....	?	?	?	
79		6		F	0	0	+	+	..	6,000- 27,000	.....	....	.....	?	?	?	
80		7		F	0	0	+	+	..	.....	.....	....	.....	?	?	?	
81		8		F	0	0	+	+	..	.....	.....	....	.....	?	?	?	
82	Levy	..	13	F	0	+	+	+	0	40,000- 86,000	16.0-63.0	....	5.0-59.0	?	3 mo.	?	Boils
83	Gittins and Hawksley	..	11 mo.	F	—	+	—	20	250	6,000- 24,500	7.0-20.0	....	0.3-0.4?	+	12 wk.	+	Ovarian tumors
84	Osgood and Lyght	..	18	M	+	+	+	+	0	3,900- 15,500	15.0-81.0?	....	.....	?	1 mo.	+	Probably not monocytic leukemia
85	Marchal, Soulié and Mahoudeau	..	50	F	0	—	+	+	0	3,200- 20,000	1.0-60.0	....	0.0-56.0	?	4 yr.	—	Pains in bones; biopsy
86	Luzina	..	0	M	0	+	+	+	+—	9,200- 35,000	38.5-75.5	....	.....	?	3.5 mo.	+	Cutaneous lesions; cerebral hemorrhage
87	Weissenbach, Bourdillon, Martineau and David	..	20	M	0	+	+	0	—	60,000- 80,000	89.0-98.0	....	.....	?	3 mo.	—	
88	Neves and Roberto Chaves	..	34	F	+	+	+	+	—	5,500- 51,300	2.0- 4.0	64.0-84.0	5.0-10.0	?	24 days	..	Cerebral hemorrhage; hematuria
89	Forkner	1	31	M	+	+	+	+	+	34,000-150,000	88.0-96.0	....	.....	+	18 mo.	+	
90		2	35	M	+	+	+	+	+	19,500-364,000	71.0-95.0	....	.....	—	6 wk.	+	
91		3	40	M	+	+	+	+	+	72,000-242,000	85.0-98.0	....	.....	+	11 wk.	+	
92		4	26	M	+	—	+	+	+	52,700- 73,500	77.0-81.0	....	.....	+	2 wk.	+	
93		5	16	F	+	+	+	+	+	74,200-160,000	67.0-94.0	....	.....	+	5.5 mo.	—	
94		6	32	M	+	+	+	+	+	71,000-110,000	65.0-88.0	....	.....	?	3 mo.	—	
95	Foot and Olcott	..	2¾	F	+	+	+	310	1,130	2,900- 9,000	0.0- 4.0	....	.....	?	14 mo.	+	Biopsy
96	Labbé, Boulin and Balmus	..	29	M	+	0	0	—	—	28,000- 30,800	54.5-59.0	....	.....	?	2 mo.	—	Boils
97		..	67	M	0	0	+	+	+	6,400- 23,000	18.0-24.0	....	0.0-13.0	?	7 mo.	—	Biopsy

98	Gregg	..	58	M	+	—	+	625	2,050	2,650- 13,200	10.0-80.0	....	.....	?	?	+	Boils; arthritis
99	Levine	1	65	F	+	0	+	1,000	2,250	8,500- 39,000	12.0-34.0	....	9.0-45.0	+	7 mo.	+	
100		2	69	F	—	—	—	150	1,500	3,000-120,000	16.0-38.0	....	14.0-42.0	+	7 mo.	+	
101		3	54	M	+	0	+	500	2,500	14,800- 30,400	38.0-58.0	....	7.0-23.0	+	2 mo.	+	
102		4	28	M	+	+	+	190	1,300	7,200	50.0	....	28.0	+	6 wk.	+	Chinese
103		5	41	M	—	+	—	950	2,250	46,450	66.0	....	5.0	?	2 wk.	+	
104		6	46	F	+	—	+	260	1,900	84,800-113,200	70.0	....	15.0	+	3 wk.	+	Negro
105		7	68	F	—	+	—	—	—	461,000	43.0	....	52.0	+	1 mo.	—	
106		8	37	M	0	—	+	+	+	1,000- 84,000	79.0	....	12.0	+	3,5 mo.	—	Sternal puncture
107		9	23	F	—	—	—	+	0	7,400- 21,600	. 19.0	....	71.0	+	3,5 mo.	—	
108	Doan and Wiseman	1	66	M	+	—	—	260	—	8,000- 90,000	36.0-80.0	....	.....	?	1 yr.	+	
109		2	63	M	—	+	+	+	+	1,500-130,000	1.5-95.0?	....	.....	?	5 mo.	+	Cutaneous nodules
110		5	0	F	0	0	0	0	0	1,200-200,000	14.0-98.0?	....	.....	?	6 mo.	?	
111		6	34	F	+	0	+	+	—	42,000-110,000	70.0-88.0?	....	.....	?	6 wk.	+	
112		7	5	M	+	+	+	+	0	7,200- 50,000	49.0-98.0?	....	5.0	?	3.5 mo.	—	
113	Morgan and Hsu	..	34	M	+	+	+	310	1,790	21,200-338,000	97.0-99.0	....	.....	+	3.5 wk.	+	Chinese
114	Marchal, Brun and Grupper	..	30	M	0	0	+	+	+	15,600- 35,400	5.0-80.0	....	5.0	?	4 mo.	+	Biopsy
115	Penati and Levi	1	38	F	+	+	+	300	1,400	3,700- 70,900	8.0-77.0	0.4-2.2	0.4-1.6	?	7 mo.	+	Sternal puncture
116		2	42	M	+	0	+	—	—	4,700- 8,200	1.6- 5.6	6.0-19.5	1.2-9.5	?	2 mo.	—	Sternal puncture; necrotic angina
117	Giffin and Watkins	1	33	M	0	0	—	1,050	+	2,600- 8,200	1.5-26.0	....	.....	?	.....	..	Still living; splenectomy
118		2	50	M	0	0	—	800	+	2,000- 4,600	2.5-22.0	....	.....	?	17 mo.	—	
119	Marchal, Lemoine and Bloch-Michel	..	73	M	0	0	+	300	+	10,500- 65,600	52.0-92.0	....	.....	?	2 yr.	+	
120	Whitby and Christie	..	44	F	+	+	+	—	+	3,400-320,000	5.0-73.0	....	0.0-42.0	+	1 yr.	+	
121	Haining, Kimball and Janes	..	34	F	—	0	0	+	0	0	75.0-90.0	....	.....	?	5 mo.	+	Rectal tumor producing intestinal obstruction
122	Mercer	1	39	M	+	0	+	+	0	21,500- 40,000	41.0-54.0	....	1.0-7.0	?	2 mo.	—	Cutaneous nodules; biopsy
123		2	47	F	—	—	+	+	—	42,300-210,000	83.0-97.0	....	.....	+	3 mo.	—	Lesions of skin and tongue; biopsy
124	Sedat	..	45	M	+	+	—	+	+	2,780- 11,750	37.0-54.0	....	.....	—	6 mo.	+	
125	Mann	..	57	M	+	0	—	250	1,400	90,000-125,000	69.0-81.0	....	.....	?	6 wk.	+	Cutaneous nodules; one or two lymph nodes enlarged
126	Tsudomi	..	48	M	0	0	0	0	0	11,500	63.0	....	3.9	—	7 wk.	+	
127	Hawksley	..	10	M	—	—	—	—	—	10,000- 20,000	73.0	....	.....	+	21 mo.	+	Sternal puncture
128	Osgood	1	7	F	+	+	+	120	930	1,000- 7,300	1.0- 7.0	8.0-20.0	0.0-9.0	—	30 days	+	Sternal puncture
129		2	36	F	—	+	+	+	+	3,450- 52,700	17.0-94.0	....	.....	+	6.5 mo.?	+	Sternal puncture; cutaneous lesions
130		3	62	M	—	—	—	425	2,250	38,600- 54,000	60.0	1.0	1.0	+	2 yr.?	+	Boils
131		4	64	M	—	—	—	+	—	27,100	5.0-44.0	26.5	1.5	+	2½ yr.	+	Still living after 1½ yr.; sternal puncture
132		5	76	F	+	—	—	—	0	151,000	.....	65.0	4.0	+	18 days	..	
133		6	67	M	—	+	+	+	0	21,300- 34,450	15.0-40.0	0.0-8.0	0.0-5.0	?	2 yr.	—	

until her death. A few days before death marked swelling of the gums, a temperature of 102 F. and three small subcutaneous hemorrhages over the legs were noted. Clearly detectable enlargement of the lymph nodes or spleen did not develop, and there was no bleeding from the mucous membranes.

Examination of the blood showed: hemoglobin, 74 per cent (10.21 Gm.); red blood cells, 3,640,000 and white blood cells, 151,000. The blood smears sent to me for diagnosis showed 65 per cent promonocytes and 4 per cent monoblasts (table 1). A diagnosis of acute monocytic leukemia was made.

The patient died on November 4. Permission for a necropsy was not obtained.

CASE 6.—H. S., a man aged 67, entered St. Vincent's Hospital on April 21, 1936, complaining of recurrent nosebleeds, weakness and loss of weight. He had had hypertensive heart disease for many years but was otherwise well until the fall of 1935, when he began to notice loss of weight and became progressively weaker. In March 1936 he began to have recurrent epistaxis, and the bleeding had become progressively more difficult to control. He entered the hospital on April 21 for cauterization of the bleeding areas. He was discharged on April 22 before the report of the examination of the blood made on April 21 was charted. He returned on April 29, in the service of Dr. T. Tharaldsen.[6] I saw him in consultation shortly after his admission to the hospital. He had a recurrence of epistaxis on April 24, lasting until April 26 and beginning again on April 27. The gums were not swollen, ecchymoses had appeared over the body and there was moderate enlargement of the axillary lymph nodes. The spleen was enlarged to percussion but not palpable. The data for the blood are shown in table 1. The patient was discharged from the hospital on May 6, and died at home on September 14. Permission for necropsy was not obtained.

COMMENT

The data for these cases and those previously reported are summarized in table 2. From this table it is evident that monocytic leukemia is being reported with increasing frequency. Since it is being reported more frequently and since individual investigators are reporting larger numbers of cases (I have seen 6 patients with this disorder in two years), it seems that monocytic leukemia is a more common disease than it has been thought to be. Rosenthal and Harris and Doan and Wiseman found reports of 532 cases of leukemia, from which statistics on the incidence of monocytic leukemia were calculated. From these reports it was estimated that 62.2 per cent were cases of myeloid leukemia, 32.7 per cent were cases of lymphoid leukemia and 5.1 per cent were cases of monocytic leukemia. Rosenthal and Harris have suggested that this relative incidence is about that of the various types of cells in normal blood. If this is correct, from 3 to 9 per cent (Osgood) of all the cases of leukemia should be cases of monocytic leukemia. The great rarity of plasma cell leukemia (Osgood and Hunter) tends to confirm this theory, because plasma cells are only occasionally seen in the blood.

It is evident that monocytic leukemia may occur at any age, the youngest patient reported on being 11 months old and the oldest 78

6. Dr. T. Tharaldsen, of Portland, Ore., gave me permission to report this case.

years. There was definitely a greater incidence in males (67 per cent) than in females (33 per cent).

Swelling of the gums was one of the most constant features, occurring in 80 per cent of the 88 cases in which the gums were mentioned, and when it is observed it should always lead to a serious consideration of the possibility of monocytic leukemia. It was more marked and constant than in other cases of acute leukemia, and a surprising number of the patients consulted a dentist before going to a physician. In many instances the swelling was associated with gangrenous stomatitis, similar to that in agranulocytosis, but it may precede the development of infection or may never be associated with infection.

Petechiae occurred in 69 per cent of the 80 cases in which they were searched for. They were usually associated with bleeding from the mucous membranes, especially of the mouth and nose, as is common in other types of acute leukemia.

Enlargement of the lymph nodes was less frequently noted (77 per cent of the 110 cases in which the lymph nodes were examined) than in other types of leukemia.

The spleen as a rule was moderately enlarged, being reported as palpable, enlarged to percussion or of definitely increased weight at necropsy in 84 per cent of the 117 cases in which there was a note in this regard. In a number of cases the size of the spleen was definitely recorded as normal, so that splenomegaly is not constant in this disease. The average weight of the spleen in the cases of adults in which it was recorded was 473 Gm., and the range was from 145 to 1,430 Gm. It is evident, therefore, that the usual enlargement is of moderate degree. An extremely large spleen in a patient with leukemia favors a diagnosis of myelogenous rather than monocytic leukemia.

Enlargement of the liver was almost as common as enlargement of the spleen, being observed in 66 per cent of the 90 cases in which a notation was made. The average weight of the liver in the adults in which the weight was reported was 2,047 Gm., and the range of the weight was from 1,250 to 3,240 Gm.

Other characteristic clinical findings were pallor, weakness and fever. The pallor and weakness were due to the rapidly developing myelophthisic anemia. The temperature was usually from 101 to 103 F., occasionally rising as high as 107 F.

Other symptoms that were less common but apparently definitely related to the disease were pain in the bones and joints, cutaneous lesions other than petechiae or ecchymoses and tumors consisting of monocytes. The cutaneous lesions were of two types. One consisted of nodules in the skin which were firm and painless and which on histologic exami-

nation proved to consist largely of monocytes, promonocytes, monoblasts and reticular tissue. This type of cutaneous lesion seemed to be specific for monocytic leukemia and to be different from the infiltrations of myelogenous or lymphatic leukemia. These lesions have been well discussed by Mercer. The second type of cutaneous lesion was staphylococcic infection of the skin, with multiple boils and carbuncles. Furunculosis occurred in these cases more frequently than can be explained by mere coincidence. Our case 4 belonged to this group. In the case reported by Gittins and Hawksley there were bilateral ovarian tumors consisting of monocytes, and in the case reported by Haining, Kimball and Janes a tumor surrounding the rectum produced intestinal obstruction.

The white cell counts in the 124 cases in which they were recorded ranged from 660 to 461,000. The average of the highest counts recorded in each case was 99,600. Three patients were leukopenic throughout the course, 6 showed leukopenia at times and no counts above the upper limits of normal and 6 had only normal leukocyte counts recorded, making a total of 15 cases, or 12 per cent, in which the white cell count was never elevated. In only 65 cases, or 52 per cent, was the leukocyte count consistently elevated.

The differential counts are difficult to evaluate because most authors did not segregate the immature from the mature monocytes. The actual distribution of the cells can be judged only from those reports in which promonocytes and monoblasts were listed, because in most instances in which no figures appeared in these columns many of the cells under the heading monocytes were undoubtedly promonocytes and monoblasts. If the cells were classed in monocytic leukemia as stem cells, myeloblasts or hemocytoblasts, I have arbitrarily placed them in the column marked monoblasts. It is evident, however, that the cells of the monocyte series may vary in the blood from almost none to 99 per cent and that the percentage of immature cells in the monocyte series may vary from practically none to over 95 per cent. In only 2 cases (23 and 94, in table 2) was there a true aleukemic course, with no increase in the number of mature or immature monocytes noted in the blood at any time. In a number of others there were aleukemic phases. Unquestionably more cases of aleukemic monocytic leukemia will be recorded now that sternal puncture (Young and Osgood) is coming into general use as a diagnostic method.

The average duration of the illness in the 104 cases in which it was possible to make a determination from the reports was five and one-fourth months. The shortest duration was ten days and the longest four years. If the cases are divided into those of acute, subacute and chronic involvement arbitrarily, the involvement being called acute when the duration of the illness was six months or less, subacute when

between six months and one year, and chronic when more than one year, there were 80 cases (77 per cent) of acute leukemia, 13 cases (13 per cent) of subacute leukemia and 11 cases (11 per cent) of chronic leukemia. The tendency for monocytic leukemia to run an acute course is clearly evident and is in contrast with that for lymphoid or myeloid leukemia, in which the chronic forms are more common than the acute forms.

ORIGIN OF MONOCYTES

Forkner has listed nineteen different views as to the origin of the monocyte, which clearly show the confusion that exists in regard to the origin of this cell. Undoubtedly this confusion would have been cleared up sooner if more studies of the sternal marrow had been made in cases of this type of leukemia. In our cases in which sternal punctures were made it was evident that the monocyte developed from a cell which may be called the monoblast, similar in morphology to the myeloblast. All intermediate stages (fig. 3) between the typical mature monocyte of the blood and this monoblast could be found. As a rule the material aspirated from the marrow consisted almost entirely of these blast cells, and the picture was so widely different from the normal that there could be no question that this cell was the precursor of the monocyte.

The characteristic features of the monoblast are its large size (from 15 to 30 microns in diameter), the fine chromatin structure of the nucleus, similar to that of the myeloblast but perhaps even more transparent, and the uniform presence of nucleoli. The nucleus is usually round or oval. The cytoplasm ranges from basophilic to deeply basophilic, and there is more in proportion to the size of the nucleus than in the myeloblast or the lymphoblast.

Monoblasts are difficult, sometimes impossible, to distinguish from myeloblasts or lymphoblasts. The chief point of difference is the more frequent occurrence of fine, diffuse azurophil granules in the cytoplasm of the monoblast, similar to those of the mature monocyte. Since these granules are not always present in the monoblast and the myeloblast may sometimes contain them, the morphologic appearance of the individual cell is often not adequate to differentiate them with certainty. The peroxidase stain does not assist in this differentiation, as all these cells show a negative peroxidase reaction. However, the fact that some of these cells are morphologically indistinguishable does not prove that they are actually identical; it is often impossible to tell in a smear treated with Wright's stain whether a cell is a promyelocyte type II or a prolymphocyte, but the peroxidase stain clearly shows them to be different.

Most authors have not given any characteristic name to cells intermediate between the mature monocyte of the blood and the monoblast,

while some have used the term promonocyte or premonocyte for these cells, without clearly defining it. I suggest that they be referred to as promonocytes and that a promonocyte be defined as a cell which has the characteristic cytoplasm and diffuse, fine azurophil granules of the mature monocyte, with the same irregularly shaped nucleus, having a finer chromatin structure and showing uniformly the presence of nucle-

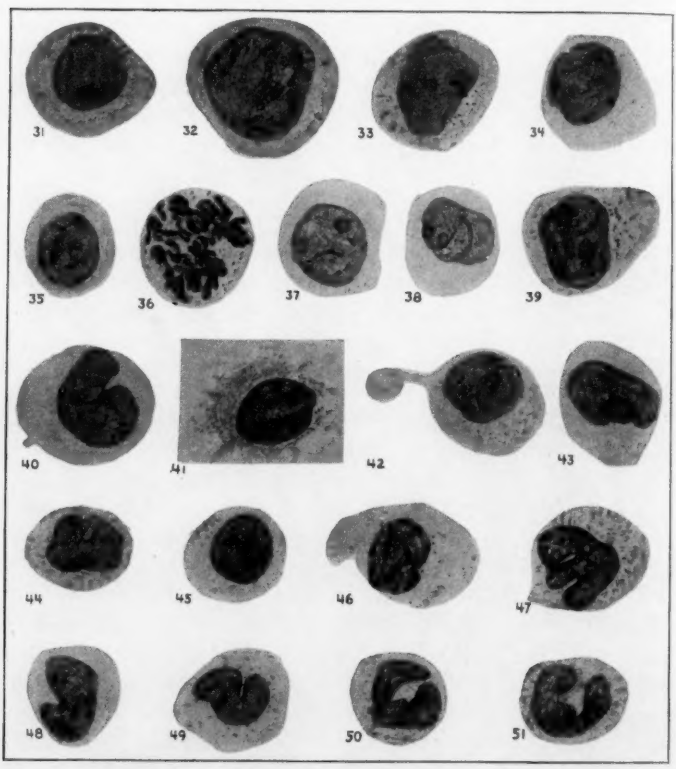

Fig. 3.—Photographs of the cells of the monocyte series (× 1,000) from the colored illustrations in the "Atlas of Hematology." The original drawings are two and one-half times the size shown here. The numbers correspond to the cell numbers in the atlas: monoblasts, 31 to 33; promonocytes, 34 to 41 (36, a cell in mitosis; 41, a disintegrated promonocyte resembling the hemohistioblast of Ferrata); monocytes, 42 to 51.

oli. As Fowler has pointed out, the nucleus of the promonocyte, with its delicate chromatin network, is often sufficiently transparent so that underlying folds of the nucleus may be seen through it. The presence

of nucleoli constitutes the major point of difference from the normal monocyte of the blood. The presence of truly round or oval nuclei with an extremely fine chromatin structure differentiates the monoblast from the promonocyte. These differences are shown in figure 3 but can be seen much better in cells 31 to 51 in the volume entitled "Atlas of Hematology" by Osgood and Ashworth, in which these cells are shown in color, magnified 2,500 diameters.

The reaction of the monocyte and of the promonocyte to the peroxidase stain varies. Even in the same specimen of blood some monocytes will show a positive reaction and others will show a negative reaction, and in many preparations no cells showing a positive reaction can be found. The most plausible explanation for this is that the monocyte itself shows a negative peroxidase reaction, but, being an extremely phagocytic cell, it frequently takes up from disintegrating granulocytes the material that shows a positive reaction. I have frequently seen this phagocytosis in cultures of marrow (Osgood and Brownlee; Osgood and Muscovitz), and there is no reason to believe that this does not occur in normal blood also.

There is good evidence that the monoblast is capable of forming reticulum, since reticulum has been found in the cutaneous lesions (Mercer) of monocytic leukemia and in the rectal (Haining, Kimball and Janes) and ovarian tumors (Gittins and Hawksley) which have been reported. There is definite evidence from studies of sternal marrow (Young and Osgood) that monocytes are present throughout life in the marrow, and undoubtedly they may be formed in the spleen in fetal life and sometimes during the course of monocytic leukemia. If they were formed normally in the lymph nodes one could expect to see them in considerable numbers in the lymph from the thoracic duct, which is not the case. It is my impression that in the present state of knowledge the terms reticulosis and reticulo-endotheliosis should not be used, as they are misleading and suggest the possession of knowledge that is not at hand. It would be equally logical to call all forms of leukemia reticulo-endotheliosis because all cells of the blood are formed in reticulo-endothelial tissue. I have never been able to find any transition in morphologic studies between the lymphocyte and the monocyte, even in material from the lymph nodes in cases of monocytic leukemia. Although I have been unable to find a method of morphologically differentiating the most immature examples of any one of the blast cells from the others, our studies (Osgood and Ashworth) lead me to believe that the monoblast, the myeloblast, the lymphoblast, the plasmoblast and the megaloblast are, in adult life, distinct types of cells, each of which can develop only into a mature cell of its own series. It is possible that cultures of marrow (Osgood and Brownlee; Osgood and Muscovitz) will definitely settle this point.

SUMMARY

Six cases of monocytic leukemia are reported, and reports of 127 other cases are cited from the literature, indicating that monocytic leukemia is a relatively common condition.

The clinical and hematologic features of these 133 cases are summarized in table 2. The most characteristic clinical features are the typically acute course, the unusual tendency to swelling of the gums and the frequent association of fever, stomatitis and hemorrhages. The most important hematologic features are the appearance of promonocytes in the blood and of large numbers of monoblasts and promonocytes in the sternal marrow.

Studies of marrow in monocytic leukemia show clearly that the mature monocyte arises from the monoblast in the marrow and develops through the stage of the promonocyte into the mature monocyte of normal blood.

The monoblast and the promonocyte are described and defined.

The term monocytic leukemia is preferable to reticulosis or reticuloendotheliosis.

The cutaneous lesions of monocytic leukemia are described, and the differences from the cutaneous lesions of other types of leukemia are pointed out.

NOTE.—Since submitting this paper for publication I have studied 3 additional cases. Twenty additional reports have been found in the literature and have been included in the bibliography.

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POISONING FROM CUTANEOUS APPLICATION OF IODINE

A RARE ASPECT OF ITS TOXICOLOGIC PROPERTIES

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Iodine was discovered accidentally by Courtois in 1811.[1] It was first used as a therapeutic agent by Coindet in 1820 in treating goiter. Its success was so great that it was soon used in many other diseases, but the unfortunate results consequent on the inhalation of the nascent fumes caused it to fall somewhat into disrepute. However, other effective uses were soon discovered. Ricord in 1836 used it in scrofula, Lugol in 1831 used it effectively in tertiary syphilis, and Wallace in 1836 published a report of a series of cases in which potassium iodide in large doses was used in the treatment of syphilis. Boinet, in 1839, was the first to use iodine as an antiseptic, employing it in various infections; he originated the injection treatment of ovarian cysts. Since that time it has been used widely, and its alcoholic solutions are recognized as some of the most effective of known antiseptics.

Iodine is probably most frequently used in the form of potassium and sodium salts. As such it is employed as an expectorant, as a diuretic, in the treatment of goiter, in the treatment of syphilis, as a contrast medium in urography and in various circulatory diseases in which there is a fibrotic or inflammatory factor, i. e., arteriosclerosis and syphilitic arteritis. The most recent use of the iodides has been in fungous infections. It has been shown that the use of iodides is contraindicated in tuberculosis, presumably because they have a direct action on devitalized, especially fibrotic, tissue and thus may be responsible for the breakdown of protective barriers. Finally, the iodides have been used indiscriminately in a wide variety of conditions, with indifferent results.

Externally, elemental iodine is employed in the form of the alcoholic solution, having long been used, as has been noted, as a cutaneous antiseptic; it is employed also for preoperative sterilization of the skin and as a counterirritant. Other uses, such as to sclerose cysts of various types and as an inhalant (in the nascent form), have largely been abandoned.

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1. Courtois, cited by Sollman, Torald: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1932.

TOXICOLOGIC ASPECT

There are two common conceptions of iodine poisoning: first, the poisoning following the ingestion of the tincture in relatively large quantities, and, second, the manifestations which occasionally follow the prolonged administration of the salts, called iodism. Nevertheless, there are, in reality, five methods by which iodine is or has been administered which may result in poisoning. These are (1) the oral ingestion of iodine or its alcoholic solution; (2) the oral ingestion of the salts of iodine, which occasionally results in iodism; (3) the inhalation of the fumes into the upper and lower passages of the respiratory tract; (4) the absorption of the tincture from a cyst into which it has been injected, and (5) the absorption of alcoholic solutions applied to the skin. Of all these, only the first is preponderantly local in its toxic effect; the others are mainly systemic.

The oral ingestion of the tincture is usually carried out with suicidal intent. Immediate gastric uneasiness, vomiting, diarrhea, with occasional bloody stools, and vasomotor collapse [1] follow. These effects are in large part due to the local corrosive action of the iodine on the alimentary mucous membrane, occurring immediately after the ingestion of the solution and allowing scant time for absorption. The fatal dose is supposed to be from 2 to 3 Gm., but much larger doses have been taken with recovery.

Iodism is a nonspecific phenomenon, as entirely analogous effects may follow the use of thiocyanates, nitrates and bromides. The manifestations are as follows:

1. Cutaneous manifestations of various sorts, including pustular and bullous eruptions, generalized erythema, purpura, urticaria and vesication—all occasionally accompanied with fever
2. Conjunctivitis, laryngitis, bronchitis and rhinitis
3. Headache
4. Stomatitis
5. Anorexia
6. Parotitis
7. Terminal cachectic states following the prolongation of symptoms and including anemia, emaciation, mental disturbances, etc.

The mechanism of these effects is still not satisfactorily explained. Fatal termination is occasionally seen.

For a long time it was thought that the direct contact of nascent iodine with various pulmonary inflammations would be beneficial. Clinical trial resulted in many mishaps, owing probably, as Luckhardt and his associates [2] proved experimentally, to depression of the blood pressure, with consequent pulmonary edema and respiratory collapse.

2. Luckhardt, A. B.; Koch, F. C.; Schroeder, W. F., and Wieland, A. H.: The Physiological Action of the Fumes of Iodine, J. Pharmacol. & Exper. Therap. **15**:1 (March) 1920.

The injection of alcoholic solution of iodine into cysts of various sorts was formerly widely practiced but has now been relegated to the limbo of discarded therapeutic measures on account of many accidents which occurred. Rose [3] first called attention to this in a report of three cases in all of which systemic reactions were present, one terminating fatally. The fatal case was that of a girl of 16. Into an ovarian cyst a solution containing 5 ounces (150 cc.) of tincture of iodine was injected. Immediately after this the patient began to vomit profusely, and she experienced extreme thirst and became cold, with a weak intermittent pulse. Parotitis then developed, associated with a diminution of salivary flow, fever, oliguria and albuminuria. Coma supervened, and the girl died in collapse. Autopsy revealed traces of iodine as iodide in the lungs and bronchi; none was revealed elsewhere. Nothnagel and Rossbach [4] collected reports of thirty-five fatal cases following the injection of the drugs into cysts.

Systemic toxic manifestations following the use of alcoholic solutions of iodine on the skin and mucous membranes are undoubtedly extremely rare, considering the widespread use of this antiseptic. Peterson and Haines [5] stated: "When applied by surgeons freely to absorbing surfaces, it [iodine] may cause systemic disturbances, such as headache, dizziness, mental trouble . . . with. . . . gastric symptoms brought out indirectly." Search of the literature reveals reports of only fourteen cases of systemic or remote cutaneous disturbances, the case presented herewith being the fifteenth. Undoubtedly there have been other cases, and probably they will become more infrequent with the increasing use of other cutaneous antiseptics at the expense of iodine. That local reactions may occur after the application of the tincture to the skin is well known, Herzog [6] having described many cases of dermatitis from its use in wounds in war time. However, Rutherford [7] noted only three cases in a total of 14,000 cases, one patient showing local ecchymosis and two showing bullae.

Iodine applied to the skin and mucous membrane is absorbed as iodide. Luckhardt and his colleagues [2] showed that the liberal application of the tincture to the skin resulted in the excretion of 4.71 mg. of

3. Rose, E.: Das Jod in grosser Dose, Virchows Arch. f. path. Anat. **35**:12 (Jan.) 1866.

4. Nothnagel, H., and Rossbach, M. J.: Nouveaux éléments de matière médicale et de thérapeutique, Paris, J.-B. Baillière & fils, 1889; quoted by deBroe.[14]

5. Peterson, F., and Haines, W. S.: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 167.

6. Herzog, W.: Zur Anwendung der Jodtinktur, München. med. Wchnschr. **61**:2319, 1914.

7. Rutherford, W. J.: Excessive Reaction Following the Use of Tincture of Iodine, Brit. M. J. **1**:846, 1915.

iodide in the urine during the following twenty-four hours. The systemic effects are probably due to iodide, as Buschke and Ollendorff's [8] patient showed a generalized eruption following the local application of iodoform; sixteen years later a similar eruption appeared after the ingestion of potassium iodide. These considerations are borne out when the symptoms of the patients who have been affected systemically by local applications are considered, but all such systemic manifestations must occur in patients who are extremely hypersensitive to iodine or who have become sensitive to it, as the quantity absorbed through the skin is relatively minute.

REPORT OF A CASE

E. H., a 52 year old man, was admitted to the medical isolation unit of the New Haven Hospital on April 4, 1936, complaining of a cold.

Three weeks prior to his admission to the hospital the patient began to experience headache, malaise, chilly sensations and pain in the chest. He began also to have a cough productive of small amounts of greenish yellow sputum which was often blood streaked. The pain was in the right anterior portion of the chest and was pleuritic. The patient believed he had three bouts of fever but had had no night sweats. Anorexia had been severe, and he had lost about 20 pounds (9 Kg.) since the onset of his illness. He became progressively weaker and finally came to the hospital for relief.

The family history was unimportant; there had been no tuberculosis in the family. The patient had married but had separated from his wife, who was living and well. There were three children living and well.

The past history was essentially unimportant. The patient had been unemployed and homeless for four years. He could remember having had only an occasional cold or sore throat. He had never had a cough previous to the onset of his present illness. He had been a house painter intermittently for thirty-five years but was fully cognizant of the dangers of working with lead and had never had a symptom of poisoning.

Physical examination revealed a well developed but rather emaciated man, who appeared to be mildly and chronically ill. The temperature was 102 F., the pulse rate 90, the respiratory rate 24 and the blood pressure 90 systolic and 65 diastolic. The skin was warm and dry and was fairly dark. There was no eruption. The head, eyes, ears and nose were normal. The teeth were discolored and carious; many were missing. The pharynx was not injected. There was no cervical adenopathy. The trachea was in the midline; the thyroid gland was small and smooth. Examination of the chest revealed diminished respiratory expansion on the right side. Over the upper half of the right side of the chest there were dulness, bronchovesicular breathing and a few coarse râles. A loud friction rub was heard in the right axilla during respiration. The heart was not remarkable. The abdomen was scaphoid, and there was moderate voluntary spasm in the right upper quadrant. The genitalia were normal. Rectal examination revealed no abnormality. The reflexes were all normal. The extremities were not remarkable. There was no generalized lymphadenopathy.

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8. Buschke, A., and Ollendorff, H.: Zur Kenntnis der Jodidiosynkrasie der Haut, Deutsche med. Wchnschr. **51**:2109, 1925.

The laboratory findings were as follows: Examination of the blood showed 4,200,000 erythrocytes, 70 per cent (Sahli) hemoglobin, 7,000 leukocytes, 70 (14 nonsegmented) polymorphonuclears, 24 lymphocytes, 3 large mononuclears, 3 eosinophils and 0 basophils. The urine was clear, yellow and acid, with a specific gravity of 1.022 and no albumin or sugar. The sediment showed a rare white blood cell per high power field. The sputum was yellow and purulent, from 5 to 20 acid-fast bacilli being seen per high power field. The stools were dark brown and solid and contained no gross blood or mucus. The reaction to guaiac was negative. The Kahn test was negative. Chemical analysis of the blood showed: nonprotein nitrogen, 32 mg. per hundred cubic centimeters; carbon dioxide, 28.4 milliequivalents; chlorides, 87.1 to 93.9 milliequivalents; total proteins, 7 Gm. per hundred cubic centimeters; albumin, 3.44 Gm.; globulin, 3.56 Gm., and sodium, 125 milliequivalents.

A roentgenogram of the chest showed extensive pulmonary tuberculosis of the upper and middle lobes of the right lung, with probable cavitation of the upper lobe, and beginning tuberculous infiltration of the left lung.

Course and Treatment.—The patient was put to bed immediately and for the next few days was merely kept under observation. During this time he was constantly febrile, the temperature ranging between 99 and 103 F. He was given ½ grain (0.03 Gm.) of codeine sulfate when necessary for his cough.

In view of the patient's asthenia, hypotension and dark skin, the question of Addison's disease was considered; for a short time studies of the blood were made, including determinations of the sodium and chloride contents, and subsequently large doses of sodium chloride were given. However, this caused no change in the patient's symptoms, and studies of the blood revealed normal values for sodium and only a slight reduction of the chloride content.

Ten days after his admission to the hospital it was decided that artificial pneumothorax was the most suitable therapy.[9] The cutaneous preparation for pneumothorax therapy is usually performed as follows: an area varying from 10 to 20 cm. in diameter is covered with full strength tincture of iodine U. S. P., and the iodine is then removed with 70 per cent alcohol. There is, naturally, some variation in the amount of iodine removed, and occasionally a fair amount remains on the skin.

Between April 16 and 29 the patient received six pneumothorax treatments, a total of 2,950 cc. of air being introduced, causing the right lung to collapse to roughly its former size. Immediately after each treatment the patient felt much worse, and in each case the temperature rose suddenly from 1 to 3 F. No physical change was demonstrable.

On April 30, the day following the sixth pneumothorax treatment, the patient's temperature rose from 100.4 to 102 F., and there was a slight reddening of the skin over the area prepared with iodine. The next day there was an extensive, confluent rash over the entire back, and on May 2 the entire body was covered with a morbilliform eruption that was confluent over the back. The mucous membranes were clear; the patient felt no worse than usual. He had been receiving codeine; this was stopped. By May 3 the rash had faded, and it was gone the

9. The isolation unit of the New Haven Hospital does not include a permanent sanatorium for tuberculous patients. Patients with tuberculosis are admitted only before the diagnosis is made or in an emergency and remain there pending their transfer to a state or federal sanatorium. Since vacancies in these sanatoriums are occasionally scarce, patients sometimes must wait as long as three months. If pneumothorax is indicated immediately, it is instituted while the patient is in the isolation unit.

next day. Another pneumothorax treatment was given on May 5, only alcohol being used for the cutaneous preparation, and codeine was resumed with no adverse results. On May 11 at 3 p. m. another pneumothorax treatment was given, and iodine again was used for the preparation of the skin. That night the temperature rose to 104 F., the pulse rate was 120 and on the following morning there was a generalized morbilliform eruption. The area of skin which had been prepared was fiery red. The rash elsewhere was maculopapular and pink, being confluent in some areas. Culture of blood taken at this time was sterile. There was moderate generalized lymphadenopathy. The mucous membranes of the mouth and eyelids were injected and covered with a thick yellow mucoid exudate. There was no bulbar conjunctivitis. Over the soft palate a hemorrhagic eruption was seen. Irrigations of the throat and eye washes were instituted. The patient was nauseated and took fluids poorly. A hypodermoclysis of 1,500 cc. was given.

On the next day, May 14, the rash was everywhere confluent; the extremities were swollen and painful to the touch. There was a thick purulent discharge from the eyes, and a profuse flow of viscid, mucoid saliva drooled from the mouth. The patient was lethargic and coughed up large amounts of greenish watery sputum. There was a leukocyte count of 14,000.

On May 15 the patient's condition was slightly worse. The superficial layers of the skin on the back began to peel off in large sheets.

On May 16 the patient was disoriented. There was beginning desquamation of the extremities, which were swollen, cyanotic and painful. The conjunctival and the oral discharge were more profuse. Urine at this time showed a 2 plus reaction for albumin, and the sediment contained from 3 to 5 white blood cells and 1 or 2 red blood cells per high power field. The leukocyte count was only 7,650. All fluid was given parenterally. The patient became much worse during the night. On the morning of May 17 the skin was peeling from the body in large sheets, leaving great denuded areas which exuded serum, so that the bed was constantly wet. Speech was thick, and coma became progressive. There was incontinence of urine and feces. There was, however, marked oliguria. The nonprotein nitrogen content at this time was 38 mg. per hundred cubic centimeters. The patient's condition rapidly became worse, Cheyne-Stokes respiration was present and in spite of appropriate stimulating measures the patient died.

Postmortem Examination.—The autopsy was performed the following day by Dr. Robert Tennant. The anatomic diagnosis was (*a*) primary: extensive exfoliative dermatitis, exfoliative pharyngitis, tracheitis, esophagitis, glossitis and acute bronchitis; (*b*) secondary: bilateral chronic ulcerative and proliferative pulmonary tuberculosis, bilateral fibrous pleural adhesions, air in the right pleural cavity (artificial pneumothorax) and tuberculous ulcer of the cecum.

The summary of the protocol is as follows:

The body was that of a well developed but poorly nourished man. The weight of the body was 44 Kg., and the length was 173 cm.

There was extensive exfoliative dermatitis over all parts of the body. The superficial layers of skin were denuded, leaving large gray-red granular surfaces. Around the face and mouth a dark yellowish green material, which appeared to be a mixture of serum and fibrin, was adherent. There was exudative material over the entire body; the back was practically denuded of epithelium. In regions where the skin was not removed there was a diffuse macular rash, the macules being red and smooth. The eyelids were glued together with a yellow-green mucoid exudate, which covered the face. The conjunctivae were reddened. There was pus at the external nares and on the lips. The body was emaciated, there being practically no subcutaneous fat. There was no adenopathy.

On section the peritoneum appeared normal over the visceral surfaces. The spleen was enlarged. There was no fluid in either pleural space. The right lung was partially collapsed, fibrous adhesions binding portions of it to the wall of the chest. The left lung was intact, but an occasional firm nodule could be palpated. The pericardium was smooth and contained 10 cc. of clear fluid.

The heart weighed 237 Gm. and was normal grossly and microscopically.

The left lung had some fibrous adhesion over the pleural surface, over which appeared a few small, deeply pigmented scars. The cut surface was red and crepitant, and red fluid oozed from it. The bronchial mucosa was deep red.

The right lung showed many adhesions over the pleural surface. The cut surface showed an empty cavity, 5 cm. in diameter, in the apex. This had a fairly thick fibrous wall which was surrounded by several sharply demarcated yellow caseous nodules, about 0.5 cm. in diameter; several of these were seen in the middle and lower lobes also. At the anterior margin of the middle lobe there was a uniformly consolidated caseous mass, 5 cm. in diameter. About a third of the right lung showed tuberculous involvement; there was practically none in the left lung.

Microscopic sections of the wall of the cavity showed dense fibrous connective tissue, throughout which conglomerate tubercles with caseous centers could be seen. Throughout other portions of the right lung many conglomerate caseous tubercles were seen, associated with the bronchi. Sections of the middle lobe showed a necrotizing, caseous tuberculous process.

The tracheal mucosa was desquamated. The surface was covered with fibrin and polymorphonuclear leukocytes, and the blood vessels were distended with red blood cells. The mucous glands were swollen.

The spleen weighed 237 Gm., and the malpighian corpuscles were large and numerous. The stomach, duodenum, pancreas and gallbladder were normal.

The liver weighed 1,653 Gm. The surface was smooth. In several small foci that were examined microscopically the cells were necrotic and were infiltrated with lymphocytes. The total weight of the adrenal glands was 19 Gm. They were normal.

The kidneys weighed 173 and 176 Gm., respectively. There was slight cloudiness of the cortical markings, but microscopically the glands appeared normal. The testes were normal.

Examination of the brain, a small portion of the spinal cord, the rectum, the ureters and the aorta revealed no abnormality.

In the cecum there was one solitary ulcer, 3 by 0.5 cm., with slightly raised edges and a yellow granular base. Sections showed infiltration with monocytes and a few polymorphonuclears. Immediately below the base of the ulcer was a tubercle.

The superficial layers of the esophageal mucosa had desquamated and formed a cast in the lumen; this had a cooked appearance. The remaining mucosa desquamated easily, leaving a granular, reddened surface. A similar process extended into the pharynx. The tongue showed some evidence of superficial desquamation. The mucosa of the pharynx and trachea were deep bright red. There was no ulceration, but there was a yellow exudate over a few points on the surface.

Microscopically the mucosa of the tongue was almost entirely denuded. In a few places it was intact but necrotic and infiltrated with polymorphonuclear leukocytes. The submucosal blood vessels were distended with red blood cells, and the connective tissue was infiltrated with polymorphonuclear leukocytes, lymphocytes and monocytes.

Sections of the esophageal mucosa showed it to be completely desquamated; the microscopic picture of the submucosal tissue was similar to that seen in the tongue. The thyroid and parathyroid glands were normal.

Microscopic sections of the skin showed complete denudation of the epithelium, with only a few scant sheaths remaining in various areas. In some regions the superficial layers remained but appeared lifted up in blister-like formation. In the corium there was a scant, diffuse infiltration of cells, mainly lymphocytes and polymorphonuclear leukocytes, with an occasional eosinophil. In areas where the epithelium was still attached, it appeared as a pink-staining layer in which the cellular outline was barely visible.

REVIEW OF THE LITERATURE

As has been mentioned previously, there have been few cases reported in which toxic symptoms followed the cutaneous application of iodine in alcoholic solution. The cases which have been reported may be summarized as follows:

Culpeper's [10] case, which was reported in 1888, was the first one that could be found. A child of 11 suffering from eczema (?) of the legs had 2 drachms (8 Gm.) of tincture of iodine applied. There was immediate local pain, followed in twenty-four hours by lumbar and generalized pain, abdominal pain and diarrhea. A starch test showed that the stools contained iodine. (This is evidently an error, since iodine is absorbed and excreted solely as iodide.) There was no fever, but diarrhea was progressive, the stools becoming practically pure blood by the fifth day. There were anuria, priapism and extreme vertigo without mental confusion. The patient died six days after the application.

The next two cases are those cited in the textbook of Stokvis [11] and by Broe.[14] These patients had an extensive pruritic eruption and severe iodism following small local applications of an alcoholic solution of iodine, the symptoms including coryza, edema, dyspnea, headache and syncope, which persisted for several days.

The next two cases were reported separately by Bielsalsky [12] and by Moszkowicz [13] at the annual meeting of the German Surgical Congress in 1911. In both the symptoms followed the use of tincture of iodine as a cutaneous preparation for Förster's operation (section of several dorsal roots). Severe suppurative dermatitis developed, and the patients died. No further details were given in the reports.

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10. Culpeper, W. O.: Acute Iodine Poisoning, Therap. Gaz. (sect. 3) **4**:225, 1888.

11. Stokvis, B. J.: Leçons de pharmacothérapie, Paris, O. Doin, 1905, p. 213; quoted by deBroe.[14]

12. Bielsalsky: Foerster'sche Operation, Verhandl. d. deutsch. Gesellsch. f. Chir. **39**:34, 1910.

13. Moszkowicz, L.: Foerster'sche Operation, Verhandl. d. deutsch. Gesellsch. f. Chir. **39**:40, 1910.

deBroe [14] in 1911 wrote a review of these cases, including in it a hitherto unreported case of an unnamed medical officer and a case of his own. In the former case tincture of iodine (this was the preparation mentioned in the French pharmacopeial "Codex," and contained 10 per cent free iodine) had been applied to the knee for some minor complaint. The application was followed by fever, malaise, delirium and "symptoms of peritonitis," all of which lasted forty-eight hours.

Broe's own case is of great interest. The patient was a healthy soldier on whom inguinal herniorrhaphy was performed, 10 per cent tincture of iodine being used in the preparation of the skin. The day following the operation, which had been uneventful, the patient had a slight cough and a few coarse râles in the chest. An iodine dressing was applied to the chest as a counterirritant. During the following night the patient began to have intense itching of both sites where iodine had been applied (the operative site had been cleaned with alcohol after the application of iodine). On the second postoperative day there was brilliant erythema of the itching areas, which extended beyond the borders of the sites to which iodine had been applied. Slight fever, conjunctivitis and lacrimation were present. Soothing dressings were applied, but the erythema spread rapidly; moderate desquamation began to appear over the sternum. The patient became thirsty. The conjunctivitis and lacrimation became more intense, the patient began to make convulsive movements which necessitated restraint, the stools became loose and there was incontinence. The temperature rose to 40.3 C. (105 F.); divergent strabismus appeared; the patient became comatose, dyspneic and cyanotic, and death occurred on the third postoperative day. Autopsy revealed, besides the cutaneous lesions mentioned, some pulmonary congestion, splenomegaly and slight hepatomegaly, the liver weighing 2,500 Gm.

Happel [15] in 1921 reported a case of somewhat different type but one in which an extreme idiosyncrasy was shown. A woman of 50, after supravaginal hysterectomy, had less than 1 drop of tincture of iodine applied to the cervical stump for purposes of cautery; seventeen hours after the operation the patient had intense itching and burning of the skin and swelling of the face and hands. When she saw wheals on her body she said, "They used iodine on me." The nurse told her that a trinitrophenol preparation had been used on the skin, but the patient insisted that iodine had been used somewhere, saying that she had had a similar experience nine years previously after the application of tincture

14. deBroe, Patris: Intoxication iodique mortelle consécutive à l'emploi de la teinture d'iode pour la stérilisation pré-opératoire de la peau, Arch. de méd. et pharm. mil. **57**:96, 1911.

15. Happel, H. E.: A Case of Unusual Susceptibility to Iodine, J. A. M. A. **76**:1164 (April 23) 1921.

of iodine to her neck. The rash was a generalized urticaria, which was quickly relieved with small doses of epinephrine.

Bryan [16] reported the case of a man of 52 who had an abdominal operation. The skin was prepared with half-strength tincture of iodine. Twenty-four hours later an urticarial rash, moderate anuria and cerebral symptoms developed, and the patient was moderately toxic. Recovery was complete, but it was found later that his life had been despaired of on a previous occasion, after the application of iodine to an infected arm.

Rowell [17] in 1923 reviewed several cases and reported the case of a man aged 55. Half-strength tincture of iodine had been used to prepare the skin for laparotomy and herniorrhaphy. On the afternoon of the day of operation the patient's temperature and pulse rate rose, and he began to show signs of shock. On the first postoperative day fever and moderate shock persisted. He improved slowly for the next few days, his temperature falling, but on the fifth postoperative day he was much worse. The areas to which iodine had been applied had become purple, and these lesions slowly spread. The temperature rose, the patient became incontinent and hemorrhagic blebs began to appear on the extremities. The stools became watery. On the eighth postoperative day the skin of the entire abdomen was purple, and blebs were more numerous on the legs and feet. The patient became irrational and died on the ninth postoperative day; just before death purple petechiae appeared over the face and thorax. The urine was normal. Progressive anemia and marked leukocytosis were noted. Chemical analysis of the blood revealed no abnormality. The clotting time was between six and seven and one-half minutes. The autopsy showed essentially no abnormality, except for an adenocarcinoma of the stomach with local metastasis.

Clifford [18] saw a patient who, after the application of tincture of iodine to the wrist and forearm, showed local erythema and vesication, but this was followed by a scarlet urticarial erythema of the face and neck. The lesions all disappeared, but the reapplication of iodine months later to a cut finger caused vesication and the formation of bullae on the hands and arms bilaterally, with erythema of the right pectoral region.

Galli [19] in 1929 reported on a woman aged 27 who had had tincture of iodine applied to the shoulder, with sudden and dramatic results. A

16. Bryan, R. C.: One Hundred Prostatectomies, Virginia M. Monthly **48:** 338, 1921; personal communication to Rowell.[17]

17. Rowell, H. G.: The Surgical Importance of Iodine Idiosyncrasy and Poisoning, Surg., Gynec. & Obst. **36:**219 (Feb.) 1923.

18. Clifford, S. H.: Iodine Hypersensitization, Boston M. & S. J. **195:**931 (Nov. 11) 1926.

19. Galli, A.: Intossicazione acuta per applicazione percutanea di tinctura di jodio, Gazz. d. osp. **40:**1299 (Oct. 6) 1929.

TABLE 1.—*Data in Cases of Iodine Poisoning*

Author	Age, Years	Sex	Preparation of Iodine Used	Site of Application	Time Elapsing Until Symptoms Appeared	Type of Eruption	Involvement of Mucous Membranes	Constitutional Reaction	Duration of Reaction	Associated Illness	Outcome	Autopsy Observations
Culpeper [10].....	11	F	Tincture	Both legs	24 hr.	None	.....	Lumbar, generalized, abdominal pain; diarrhea with bloody stools; priapism; anuria; vertigo	6 days	Eczema of legs	Fatal	.....
Stokvis [11].....	..	..	Alcoholic solution	.....	.....	"Extensive pruritic"	Iodism	Dyspnea; headache; edema; coryza; syncope	Several days	.....	Recovery	.....
Stokvis [11].....	..	..	Alcoholic solution	.....	.....	"Extensive pruritic"	Iodism	Dyspnea; headache; edema; coryza; syncope	Several days	.....	Recovery	.....
French medical officer [14]	..	F	Tincture	Knee	.....	None	None	Fever; malaise; delirium; "symptoms of peritonitis"	48 hr.	.....	Recovery	.....
Bielsalsky [12]...	Child	..	Tincture	Back	.....	Suppurating dermatitis	.....	.....	.....	.....	Fatal	.....
Moszkowicz [13].	..	..	Tincture	Back	.....	Suppurating dermatitis	.....	.....	.....	.....	Fatal	.....
de Broe [14].....	..	M	Tincture	Inguinal region; chest	About 12 hr.	Pruritic erythema	Mainly conjunctivae	Fever; conjunctivitis; lacrimation; convulsive movements; diarrhea; strabismus; incontinence; terminal dyspnea and cyanosis	3 days	None	Fatal	Splenomegaly; hepatomegaly; pulmonary congestion
Happel [15].....	50	F	Tincture, 1 drop	Cervical stump	17 hr.	Generalized urticaria	None	None	2 days	None; postoperative hysterectomy	Recovery	.....

Bryan [16].....	52	M	Tincture, half-strength	Abdomen	24 hr.	Generalized urticaria	None	Anuria; cerebral symptoms; moderately toxic	.....	Postoperative prostatectomy	Recovery	.....
Rowell [17].....	55	F	Tincture, half-strength	Abdomen, inguinal region	6 to 10 hr.	Hemorrhagic purpura with bleb formation	None	Fever; shock; diarrhea; irrational	9 days	Carcinoma of stomach	Fatal	Essentially no abnormality
Clifford [18].....	..	..	Tincture	Wrist and forearm	.....	Scarlet urticarial erythema	None	None	.....	.....	Recovery	.....
Galli [19].....	27	M	Tincture	Shoulder and chest	Less than 5 min.	Generalized punctate erythema	Injection of conjunctivae; coryza; genital swelling	Nausea; vomiting; headache; malaise; precordial pain; dyspnea; cough; coma	More than 3 days	.....	Recovery	.....
Alexander [20]...	37	M	3.5% alcoholic solution	Inguinal region	24 hr.	Local hemorrhagic eruption	None	Fever; tachycardia; delirium	3 days	Postoperative herniorrhaphy	Death	.....
Brenas and Weis [21]	4	F	Tincture	Umbilicus	Few hr.	Brilliant local erythema; spreading; bullae	None	.....	More than 3 days	Oozing of umbilicus	.....	.....
Seymour.....	52	F	Tincture	Chest, posterior axillary region	24 hr.	Generalized erythema; later exfoliative dermatitis	Extensive	Fever; severe coryza; delirium; cyanosis; coma; incontinence	60 days	Pulmonary tuberculosis	Fatal	Pulmonary tuberculosis; exfoliative dermatitis; splenomegaly; pharyngitis; bronchitis; etc.

violent burning occurred at the site of application, and within less than five minutes the patient became nauseated and vomited. She had a violent headache, malaise, precordial pain, dyspnea and cough and experienced a sense of impending death. When Galli saw her she was comatose and dyspneic and was vomiting involuntarily; her pulse was weak and thready. After appropriate stimulation and removal of the excess iodine with alcohol, the patient slowly recovered. Three days later redness and swelling of the conjunctivae and the pharyngeal and buccal mucous membranes were noted. There was cervical and axillary lymphadenopathy. A punctate erythema covered the entire body, and there were swelling and redness of the external genitalia, especially the urethral meatus. The patient slowly recovered. The urine was shown to contain iodide. The patient had never previously used iodine in any form.

Alexander [20] reported the case of a 37 year old woman who had cutaneous preparation of 2.5 per cent iodine in alcohol twenty-four hours before herniorrhaphy was performed and again at the time of operation. On the first postoperative day some itching and redness of the prepared area were noted. On the second day the entire area was purple, with an occasional white spot. The temperature rose to 103 F. and the pulse rate to 140. The patient became delirious and died on the third day postoperatively. The urine and stools were normal, and leukocytosis was slight. There was, presumably, no autopsy.

Brenas and Weis [21] reported a case in which tincture of iodine had been applied to the oozing umbilicus of a 4 year old child. Within a few hours violent erythema appeared which spread rapidly, and within three days extensive erythematous and bullous lesions covered the entire abdomen, the chest and the inner aspect of the thighs. No mention was made of systemic disturbances.

COMMENT

The application of tincture of iodine to the skin can hardly be called a hazardous procedure, since the incidence of systemic reactions is apparently low. However, the symptoms and signs of systemic reaction, once they appear, are strikingly similar, as shown in table 1. Many of the case reports presented are, unfortunately, lacking in many essential details, but a tabulation of the available data is presented in table 2.

It may be seen that in most cases ordinary tincture of iodine was employed. The U. S. P. tincture contains 7.5 per cent free iodine, but some foreign preparations contain 10 per cent.

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20. Alexander, R. C.: Fatal Dermatitis Following the Use of Iodine Spirit Solution, Brit. M. J. **2**:100 (July 19) 1930.

21. Brenas and Weis, quoted by Bory, L.: Les iodides cutanées, Progrès méd., June 23, 1934, p. 1046.

The lapse of time before systemic reactions appear is apparently less than twenty-four hours. In one case (Galli) they appeared immediately; this patient evidently had a real hypersensitivity to iodine, and her symptoms were those of acute anaphylactic shock, followed by symptoms of iodism and a cutaneous rash. Rowell's case probably falls in this same class. In the remaining cases the lapse of time between application of iodine and systemic symptoms was greater; however, although the immediate reaction was not as pronounced, the subsequent reaction was apparently as severe as in the others.

TABLE 2.—*Tabulation of Data*

	No. of Cases	Percentage
Preparation of iodine employed		
Full strength tincture	10	
Half-strength tincture	2	
Alcoholic solution, strength not specified	3	
Time elapsing before systemic symptoms appeared		
Immediately	1	
Up to 6 hours	2	
Up to 12 hours	1	
Up to 24 hours	5	
Over 24 hours	0	
Not specified	6	
Types of eruption		
Urticarial	4	
Erythematous	4	
Hemorrhagic or purpuric	2	
"Suppurative"	2	
Exfoliative dermatitis	1	
None	2	
Involvement of mucous membranes	5	33
Principal symptoms		
Delirium	9	
Fever	5	
Diarrhea	4	
Pain	3	
Headache	3	
Edema	3	
Terminal symptoms		
Dyspnea	4	
Incontinence	2	
Oliguria or anuria	2	
Cyanosis	2	
Mortality rate	..	46.9

Two of the cutaneous rashes were definitely urticarial, two were specified as being merely pruritic, and four were erythematous; one of the latter was pruritic. The urticaria is suggestive of an "allergic" type of sensitivity, whereas the erythemas are of the type commonly associated with drug sensitivity. The two purpuric rashes were definitely suggestive of iodide reaction. Unfortunately, the rashes termed "suppurative" are not explained in detail.

The case reported in this paper is the only one in which one of the severest, if not the most severe, types of cutaneous reaction was noted, namely, exfoliative dermatitis. Whether this reaction was due to the

iodine-tuberculosis relationship is an interesting question. Lass[22] demonstrated that the intracutaneous administration of a solution of sodium iodide to normal subjects caused no reaction, whereas nine of fifteen patients with pulmonary tuberculosis so tested showed local reddening and wheal formation. The reason given for the avoidance of iodides in tuberculosis is that the iodides facilitate lysis of the tissue formed by inflammatory reaction, thus facilitating the spread of the tubercle bacilli; but Lass' work and the case of exfoliative dermatitis presented seem to indicate that there may be other factors which must be taken into consideration. The fact that the patient with exfoliative dermatitis did not show any reaction to iodine until several applications had been made suggests that sensitivity was being established which finally manifested itself in severe cutaneous and systemic disturbances.

In five of the fifteen cases coryza was associated with iodism, thus making it conclusive that the reaction was due to iodine. As has been stated previously, these persons must have been extremely sensitive, as the total minimal dose of iodine in the form of potassium iodide required to produce symptoms of iodism is from 60 to 75 grains[1] (3.8 to 4.8 Gm.), and in these persons milligram quantities were used.

To attempt to explain the symptoms and signs in these cases would be entering the realm of pure speculation. The usual explanation of the cause of death when large doses of iodide have been employed is that the iodide alters the colloidal equilibrium of the blood. That explanation is not tenable in the cases presented here, as the concentration of iodide in the blood stream must have been relatively minute. I believe that in the present case death was attributable to the exfoliative dermatitis.

SUMMARY

A case is presented in which there were several local and general cutaneous manifestations and severe systemic symptoms, including iodism, following repeated local applications of tincture of iodine to the skin, and which terminated fatally after the development of exfoliative dermatitis.

A survey of available literature shows reports of fourteen cases of hypersensitivity to cutaneous applications of an alcoholic solution of iodine to the skin. Toxic manifestations were cutaneous and systemic. The mortality rate was 46.9 per cent.

22. Lass, E.: Jod- und Histaminempfindlichkeit der Haut bei Tuberkulösen, Ztschr. f. Tuberk. **67**:350, 1933.

CHRONIC RELAPSING LATENT MENINGEAL PLAGUE

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Plague has become a permanent problem in the western states.[1] In fact, the investigations of 1935 and 1936 have conclusively shown that the endemic reservoir in the ground squirrel (Citellus beecheyi), first suspected in 1904 and proved in 1908 in California,[2] now embraces large territories and new species of rodents (Citellus oregonus, Citellus armatus, Citellus Columbianus, Citellus grammurus, Citellus Richardsoni, Marmota flaviventris, Eutamias quadrivittatus and Cynomys parvidens) in Oregon, Idaho, Nevada, Utah and Montana. Renewed interest created by the discovery of extensive and destructive epidemics among squirrels in the foothills of the Sierra Nevadas and the recesses of the Warner Mountains in northeastern California in 1934 has doubtless been responsible for the recognition of a few cases of plague in human beings. These infections must be interpreted as accidents, as they involve occupational groups or vacationists who have in one way or another come in contact with animals. Thus, a sheep herder, who in 1934 was employed on a desert near Lakeview, Ore.,[3] contracted bubonic plague. In 1935 a 10 year old boy in California and a 7 year old boy in Utah had bacteriologically proved "pestis minor infections" of the axillary lymph nodes after handling brush rabbits or squirrels. Another case of plague in a veterinarian is interesting from an epidemiological point of view, since the sources of Pasteurella pestis have not been conclusively established, although newer knowledge indicates a much wider distribution of infected fleas than was formerly anticipated. It is our purpose in this communication not to discuss the many riddles

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1. Meyer, K. F., and Eddie, B.: California & West. Med. **43**:399, 1935.
2. Wherry, W. B.: J. Infect. Dis. **5**:485, 1908.
3. Levin, William: Northwest Med. **34**:161, 1935.

which the problem of plague in wild rodents—sylvatic plague—offers in its relations to man but to present the history of a patient with chronic bubonic plague with latent meningeal localization and death on the one hundred and twenty-first day after onset and isolation of fully virulent P. pestis from the brain and its coverings. In all probability the boy contracted the infection while playing in an area in which rodent plague was epizootic. The history briefly is as follows:

REPORT OF A CASE

History.—C. P., a boy aged 10 years and 5 months, was admitted to the University of California Hospital on Oct. 15, 1934. He died on October 22. The chief complaint was fever, anorexia and vomiting of one week's duration after convalescence from bubonic plague.

The family history was essentially unimportant.

The patient lived on a ranch about 5 miles (8 kilometers) north of Porterville, Calif. On June 1 the family went to a ranch 10 miles (16 kilometers) beyond White River in the Posey Creek country, which is in a plague area. On June 19 the boy complained of being ill with nausea and vomiting; he had a high fever and was delirious at times. No diagnosis could be made by the local physician who saw him at that time. On June 20 the fever continued to be high. He was still irrational at times and complained of double vision. He was considerably troubled with mucus in the throat and some pains in the right shoulder.

About noon on June 21 he was brought home and put under the care of Dr. Walter W. Tourtillott. At that time the temperature was 104 F. The patient seemed confused mentally and had definite diplopia, a rapid, thready pulse and a normal respiratory rate. He complained chiefly of pain in the shoulder, particularly in the axillary region. The right axillary fossa was fuller than the left, and a large painful node (the size of a walnut) was palpated. It was definitely tender. The reflexes were normal and equal. There was no suggestion of a Kernig sign or stiffness of the neck. There was no rash of any sort. The throat was reddened, and the tongue was coated. No other physical findings were noted, except possible hoarseness. During the day, with forcing of fluids and flushings, the fever subsided somewhat, and it seemed that the general condition improved. The boy was given 50 cc. of whole blood from his father, on the assumption that the disease might be anterior poliomyelitis.

When seen at 1 p. m. on June 22 the boy did not seem to be acutely ill. He was entirely rational, and there was nothing unusual about his voice. The fever was slight (the temperature being 100 or 101 F.), and the quality of the pulse was good. He was perspiring moderately, but owing to the weather this probably was not unusual. Casual inspection revealed no difficulty in breathing, no signs of rash or injury and nothing unusual except a tendency to protect the right axilla and limit the motion of the right arm. The reflexes were normal, and there were no signs of muscle weakness. The right axilla bulged slightly, and a few small nodes (the size of a pea) could be palpated. The axillary region was still tender. The submaxillary, anterior and posterior cervical, left axillary and inguinal lymph nodes were not palpable. On the right cheek at the angle of the mandible a small lesion, apparently an insect bite, was noted. The boy said that a "kissing bug" had bitten him there about a week previously. Blood smears were made, and blood for culture and agglutination was taken.

On June 24 the boy's temperature rose to over 105 F. On June 25 it was over 106 F., and on the morning of June 26 it reached 107.6 F. rectally, with a septic swing. Even with the high fever the boy was only mildly confused. Dehydration was not marked. The appearance of the right axilla had changed considerably. The skin presented a reddened brawny induration, and the underlying tissues were tense, swollen and exceedingly tender. The patient cried out with every movement of the right arm. The cervical lymph nodes on both sides were swollen, tense and painful.

A blood count made at that time in a local laboratory showed 20,000 leukocytes, with 95 per cent polymorphonuclears, 64 per cent hemoglobin and 3,450,000 erythrocytes. A blood culture in dextrose broth also was made, and as the boy was raising some thick mucus, a specimen of sputum was examined.

On June 27 Dr. W. H. Kellogg, chief of the bureau of laboratories of the state department of public health, reported that he had succeeded in isolating a pure culture of the plague bacillus from the blood cultures.

The swelling under the arm receded at first and then became more noticeable, the edema extending down the side. On June 29 redness developed along the tendons of the biceps, and the abscess opened spontaneously, exuding a thick, gelatinous pus. Smears of this pus were nearly solid with P. pestis. This bubo continued to discharge until about September 1, when it healed. The nodes in the neck receded without suppuration. No enlargement of the spleen or liver was evident at any time.

At the end of about three weeks (on July 16) the child again became severely ill (fig. 1) and complained of a stiff neck and pain in the back. He had a headache, and the Kernig sign was present. He became unconscious. Spinal puncture showed 105 leukocytes, with 80 polymorphonuclear cells. At that time smears and cultures were sterile. During this period the boy was given saline and dextrose solution intravenously and rectal feeding. He gradually improved until September 13, when the temperature became lower and he was sitting up in bed, eating well and gaining weight. On September 13 the quarantine was raised, and the nurses were dismissed. The patient still had a low grade septic temperature, but the improvement was so marked that it was felt that the danger of contagion had passed and that the parents could care for him.

During the first week of October (October 8) he again became acutely ill. This attack was characterized by a high temperature, delirium at times, vomiting, headache in the frontal and suboccipital region and rigidity of the neck.

On entrance to the hospital, eight days later, he was emaciated and showed marked tremor of the hands and feet, fibrillary muscle twitching, marked hyperesthesia and extreme pallor. There were sordes on the gums, slight general lymphadenopathy, healed scars in the right axilla and healed areas over the back. The heart and lungs were essentially normal, and the spleen was palpable just below the costal margin. All the deep reflexes were hyperactive but apparently equal. There were unsustained clonic ankle movements, generalized ataxia of the hands and slight cervical stiffness, and there seemed to be definite mental confusion, with, at times, complete aphasia.

Laboratory Data.—Tests showed that the blood of the patient was of type II; that of the father, of type II, and that of the mother, of type IV. The blood of the parents was compatible.

On October 20 examination of the spinal fluid revealed that it was yellow and under increased pressure. It contained 425 cells, with 84 per cent lymphocytes, and

the Pandy reaction was 4+. Direct smear showed short gram-negative rods. On October 21 there were 352 cells, with 82 per cent lymphocytes, and the Pandy reaction was 4+. A smear showed the same organisms as had the previous specimen.

When the patient was admitted a blood count showed: hemoglobin, 98 per cent; erythrocytes, 6,590,000; leukocytes, 11,900, with neutrophils 70 per cent, eosinophils 2 per cent, basophils 1 per cent, small lymphocytes 11 per cent, large lymphocytes 5 per cent, large monocytes 6 per cent and myelocytes 6 per cent. On October 17 a blood count showed: hemoglobin, 95 per cent; erythrocytes, 4,990,000, and leukocytes, 13,800, with 94 per cent neutrophils. The blood serum in a dilution of 1:320 agglutinated a strain of P. pestis (in a solution of formaldehyde).

Chemical analysis of the blood showed: carbon dioxide content of the plasma, 62.5 volumes per cent; plasma chlorides, 553.41 mg. per hundred cubic centimeters; serum calcium 10.6 mg., and serum phosphorus, 3.14 mg. Urinalysis revealed no abnormality.

Treatment.—Transfusions, continuous intravenous injection of dextrose, clyses and sedatives were employed.

Course.—The patient was in a critical condition on entry and in spite of symptomatic therapy continued to fail, having periods in which his condition seemed to be improving but after which he would again lapse into unconsciousness. Although he was afebrile for the first few days, his temperature continued to rise and reached 41.5 C. (106 F.) at the time of death on October 22, one hundred and twenty-one days after the onset of the illness.

Gross Postmortem Examination.—The autopsy was performed four hours after death. Only the significant observations will be given here.

Skin: The skin over the back, especially in the lumbar region, was marked by numerous small scars resembling healed abscesses. There were scars likewise in the right axilla.

Lymph Nodes: The mesenteric lymph nodes and other lymph nodes throughout the body were essentially of normal size.

Spleen: The spleen was moderately enlarged, weighing 200 Gm. It was dark blue-gray and soft, with rounded edges. The cut surface was red and mushy, and considerable pulp could be scraped off with a knife. Except for purulent bronchitis and early bronchopneumonia, the only other pathologic condition, in addition to that in the spleen, was in the brain.

Brain: The dura was tense, and the convolutions were markedly flattened, indicating that there had been marked intracranial pressure. The pia-arachnoid was thickened and opaque, particularly in the region of the pons, the inferior portion of the cerebellum and the base of the cerebrum. The lateral and third ventricles were markedly distended with cloudy, slightly yellowish fluid. A thick gelatinous exudate was attached to the walls of the lateral ventricles. The choroid plexuses were particularly reddish gray, soggy, swollen and covered with an exudate similar to that in the other portions of the ventricles. The aqueduct of Sylvius, below the level of the superior colliculus, appeared to be occluded by white and somewhat granular tissue resembling the exudate in the ventricles. The fourth ventricle contained numerous small punctate hemorrhages. The spinal cord, below the medulla, appeared to be normal.

The significant gross features, therefore, were the moderate enlargement and softening of the spleen and the intense swelling of the brain, due to internal

hydrocephalus and ventriculitis, with the exudate in the pia-arachnoid at the base. In addition, the bone marrow of the femur was dark red and hyperplastic. The lymph nodes had returned to normal size.

Microscopic Postmortem Examination.—Spleen: The spleen throughout had the appearance of early autolysis, resembling to some extent an infarcted spleen; that is to say, the cells and tissue in general did not stain as normal cells should. The splenic corpuscles were remarkably small, and the lymphoid cells comprising them were scattered for some distance into the pulp. The sinusoids were markedly distended with red blood cells and contained an increased number of monocytes and polymorphonuclear cells. The pulp, in general, was definitely increased. The change was not marked enough to be typical of acute plague, but there was a definite resemblance. It looked like an early rather than the late change one might have expected.

Brain: Sections from the cortex showed moderate cellular infiltration into the meninges, and in places these cells followed the blood vessels into the cortical tissue. Sections from the lateral ventricle showed marked cellular infiltration beneath the ependyma. Many of these cells were young mononuclear cells resembling lymphocytes; others were macrophages, and a few polymorphonuclear cells were seen. Adjacent to the ventricular wall there was marked necrosis of the cortical tissue, associated with macrophage infiltration and round cell accumulations around the blood vessels (fig. 2). A section of the choroid plexus showed remarkable infiltration with the same types of cells described, with a thick exudate on the surface of the plexus (fig. 3). Other sections showing the pons, aqueduct of Sylvius and fourth ventricle indicated that the infection had passed throughout the ventricular system and in all places had infiltrated beyond the surface of the ependyma. Everywhere there was the necrosis described in the neighborhood of the lateral ventricle. The most pronounced meningitis was in the region of the pons and cerebellum.

Bacteriologic Postmortem Examination.—Culture of material from the axillary lymph nodes was sterile. Culture of pulp from the spleen showed five colonies of cocci. The heart blood was sterile. Culture of bronchial mucous parenchyma showed staphylococci, streptococci and diphtheroid bacilli.

Spinal fluid removed from the right ventricle and centrifugated showed sediment on blood agar slants. There were numerous gram-negative bipolar, pleomorphic rods. Pure culture of the spinal fluid was agglutinated by P. pestis antiserum and biochemically behaved like P. pestis.

A guinea-pig inoculated percutaneously with culture lost weight. When killed on the seventh day the animal showed left inguinal and iliac buboes and several metastatic lesions in the liver and spleen. Culture revealed P. pestis.

The choroid plexus was emulsified in broth (10 per cent) and injected subdurally into two guinea-pigs (left side). The first animal showed left hypopyon, a loss in weight and anorexia. It was killed on the thirteenth day and showed leptomeningitis; left hypopyon; submaxillary, cervical and left axillary buboes, and metastatic nodules in the lungs, spleen and (one only) liver. P. pestis was isolated bacteriologically and culturally from the brain, eye and lymph nodes. The second guinea-pig showed typical plague marasmus. It was killed on the seventeenth day and showed cervical, submaxillary and auricular buboes, leptomeningitis and metastatic nodules in the spleen (two only) and liver (one only). Cultures of material from the lesions yielded a few colonies of P. pestis.

The strain of P. pestis isolated from the meninges of this patient when passed by the cutaneous route fatally infected guinea-pigs in four or five days. In

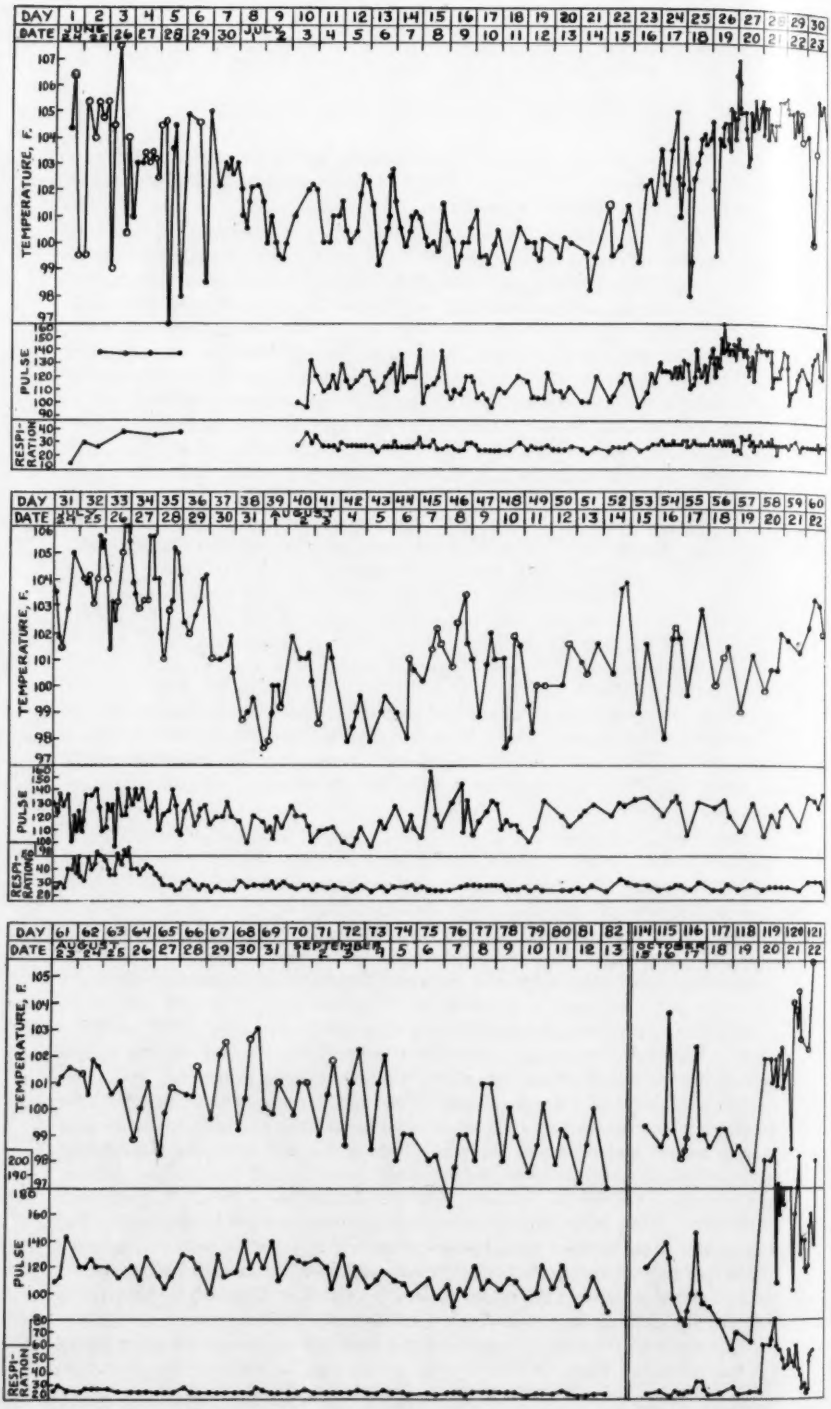

Fig. 1.—Clinical record of C. P., aged 10 years, of Tulare County, Calif., who had bubonic plague. From September 13 to October 15 no record was available. The black dots in the graph for the temperature indicate oral readings, and the circles indicate rectal readings.

Fig. 2.—Photomicrograph showing the ependymal surface and subependymal tissue of the lateral ventricle. Most of the ependymal cells have sloughed away, and cellular infiltration and necrosis of the underlying tissue and perivascular accumulations of cells as in acute encephalitis are noted.

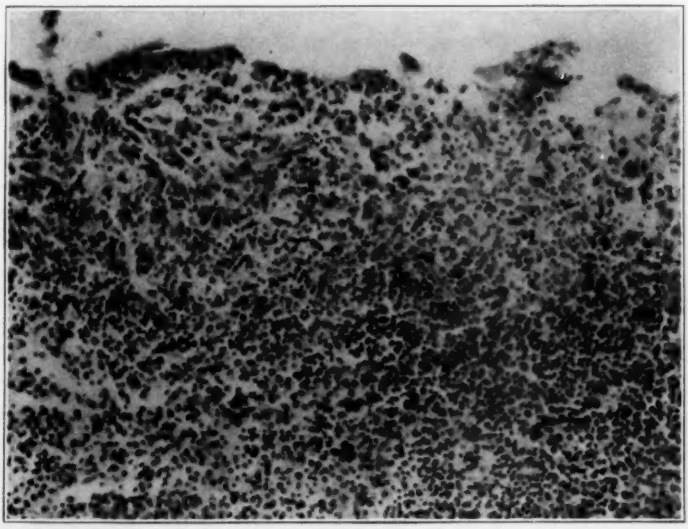

Fig. 3.—Photomicrograph of the remarkably thick exudate in the choroid plexus of the lateral ventricle.

comparison with other cultures of P. pestis of squirrel origin, the human strain possessed an average degree of infectiousness.

Diagnosis.—In view of these observations the following diagnosis is fully justified: chronic bubonic plague of a secondary latent meningeal type contracted through a flea bite while the patient was near White River (Posey Creek) some time between June 5 and 18, 1934.

COMMENT

In the past in the clinical and anatomic descriptions of plague the disease process has been classified, according to mildness or severity, as pestis minor, pestis major and pestis siderans or pestis fulminans. Cases of pestis minor included cases in which there was mild involvement, always ending in recovery, while cases of pestis major comprised those of severe pestis fulminans, with a rapidly fatal course. The classification now adopted is one which is based more or less on the particular system of the body invaded by the plague bacillus. Thus, plague is reported as bubonic, septicemic and pneumonic, according to whether the glandular, circulatory or respiratory system is involved. In addition, a description of the carbuncular, intestinal and cerebral types is given sometimes in order to stress certain pronounced systems. After all, these classifications are based on artificial descriptions, representing merely different signs or degrees of one disease, all the cases including main features of a common likeness. In 70 to 80 per cent of cases buboes are noted, and provided an adequate sample of blood is taken, the plague bacillus may be demonstrated in the circulatory system. On the other hand, in a septicemic type pneumonia may develop and become septicemic or bubonic or both. It must be emphasized that there are few diseases which present a greater variety of manifestations than plague. As it may show variations from a mild to a severe attack, from a prolonged illness to death within a few hours or from a malady accompanied with great mental aberration to one with many of its diagnostic symptoms absent, there is frequently difficulty in realizing at first that a patient is suffering from infection with P. pestis. For descriptive purposes plague may be clinically divided into plague with buboes and plague without buboes. Again, this distinction is not accurate, since in all forms of plague the lymphatic system is more or less affected; and although this may not be recognized during life, it is invariably observed post mortem. Frequently superadded to the symptoms peculiar to the several varieties of plague are disorders of the nervous system, notably paralysis of the vagus and recurrent nerves. Aphasia, ataxia, dementia and hysterics are most common; and although they are generally temporary, they may become permanent. Signs of meningismus due to an increase in the spinal fluid pressure have frequently been reported. As early as 1899 Calmette and Salimbeni called attention to the clinical dis-

tinction between the occasional nervous symptoms caused by the toxins of P. pestis which accompany all forms of plague except the most mild and those induced by the direct localization of the organism in the meninges or in the brain substance. They fully corroborated the previous observations of Griesinger [4] and others made on patients with pronounced psychic symptoms but no actual cerebral infection. A perusal of the available histories on plague leaves no doubt that true meningitis is rare. Moreover, when the condition has been found, it has been acute, and the infection has not lasted for longer than one month. The following case reports, presented chronologically, are available:

The Austrian Commission (Albrecht, Ghon and Müller [5]) reported on a series of 80 clinical cases (with 48 autopsies) in which there was 1 case of plague meningitis.[6]

A 35 year old Hindu was admitted to the hospital on the tenth day of illness. He was free from headache or stiffness of the neck. On the twelfth day clonic twitching and a disturbed sensorium developed. Death occurred on the fifteenth day. Examination of the brain revealed a clumped purulent exudate in the vicinity of the pons and on the surfaces of the cerebellum. The meninges were edematous and dull. The ventricular fluid was turbid with yellowish flakes, and the thickened plexuses were covered with a greenish yellow exudate. The brain substance was soft and sparsely studded with hemorrhages. Plague bacilli were demonstrated bacteriologically and by culture.

The German Indian Plague Commission [7] (1897), in a series of 376 histories, listed 4 cases in which there was meningeal localization of P. pestis.

Case 1.—A 16 year old boy died on the third day of illness with meningitis. At autopsy the dura was tense, and hemorrhages were present. The veins of the meninges were filled with blood, and in the region of the frontal lobes they were embedded in turbid whitish yellow gelatinous fluid. The brain was covered with cell-rich bloody material. The basal ganglions were dark gray-red. In the pons and medulla were large petechiae, and the ventricular surfaces were injected.

Case 2.—A woman of 30 died on the twenty-second day of illness. Separation of the meninges revealed a cell-rich exudate. The organisms were isolated in culture. The dura was tense. The sinuses were filled with dark violet blood. The inner surface of the dura was shiny, and the pia mater was congested. This was also the case with all the blood vessels. The lateral ventricle supplied about 30 cc. of yellowish serum. The choroid plexus was pale red.

Case 3.—A 13 year old girl died fifteen days after the onset of illness. At autopsy essentially the same lesions were noted as in the other cases.

4. Griesinger, W., in Virchow, R.: Handbuch der speciellen Pathologie und Therapie, Erlangen, F. Enke, 1857, vol. 2, p. 217.

5. Die Beulenpest in Bombay im Jahre 1897, Denkschr. d. k. Akad. d. Wissensch. Wien. (pt. 1) **66**:122; (pt. 2) 287, 1898.

6. Footnote 5, pt. 1, pp. 122 and 197; pt. 2, p. 287.

7. Bericht über die Thätigkeit der zur Erforschung der Pest in Jahre 1897 Indien entsandten Kommission, Arb. a. d. k. Gsndhtsamte. **15**:16, 1899.

CASE 4.—Meningitis and encephalomeningitis were present in this case. Only the anatomic diagnosis was made. The age of the patient, the duration of the illness and other details were not given.

Calmette and Salimbeni [8] recorded 3 cases, 2 accompanied with meningitis and 1 with meningo-encephalitis.

CASE 1.—A woman with meningitis entered the hospital on the seventh day of illness and died two weeks later. At autopsy the lesions at the base in the meninges were in the nature of a fibrinous exudate in the process of organization. In the exudate rare organisms were observed, but culture gave many colonies.

CASE 2.—A child aged 7½ years entered the hospital on the second day of illness with a right inguinal bubo. There were all the characteristic symptoms of meningitis—opisthotonos, strabismus, dilatation of the pupils, delirium, cramps in the tendons of the arms, flexion of the limbs and fibrillary movements of the muscles of the face. This patient was treated with serum, and ten days later the buboes were incised. Perfect recovery followed.

CASE 3.—A man of 25 entered the hospital with a right inguinal bubo. He was in a wildly delirious state which necessitated control by force. The next day and night there were hallucinations of sight and hearing, and he was unable to recognize friends. The next night he fell into a comatose state and died. At autopsy generalized meningo-encephalitis was present. The subarachnoid spaces were severely affected and contained many plague bacilli. The gray as well as the white substance of the cortex was greatly congested. There was mild edema of the entire cerebrum.

In a series of 16 autopsies Dürck [9] noted 1 case of primary plague pneumonia associated with fresh purulent leptomeningitis. Lafont, Lecomte and Heckenroth [9a] examined a native of Dakar, French West Africa, who had been picked up unconscious. The spinal fluid consisted of thick ropy purulent yellow exudate teeming with plague bacilli. The patient died twenty-four hours after entrance into the hospital. The careful report by Crowell [10] on 75 autopsies details the histories of the following cases of plague meningitis:

CASE 1.—An 18 year old boy was said to have been ill for a month. Autopsy revealed cervical retropharyngeal buboes, bronchopneumonia, acute parenchymatous degeneration of the viscera and acute splenitis. The description of the brain is given verbatim: "The meninges over the hemisphere are dry, and the convolutions are flattened. At the base of the brain, about the circle of Willis and ventral to the pons, is found considerable greenish-yellow pus. The lateral ventricles contain a turbid, slightly greenish fluid mixed with a thick, stringy, greenish-yellow pus, which is adherent to the floor of the ventricles, especially at the region of the

8. Calmette, A., and Salimbeni, A. T.: Ann. Inst. Pasteur **13**:865, 1899.

9. Dürck, H.: München. med. Wchnschr. **49**:550, 1902.

9a. Lafont, A.; Lecomte, A., and Heckenroth, F.: Bull. Soc. path. exot. **8**:92, 1915.

10. Crowell, B. C.: Philippine J. Sc. **10**:301, 1915.

choroid plexus, which is completely enveloped in the exudate. The floors of the ventricles are thickly covered by this shaggy mass. The third and fourth ventricles contain a slightly turbid fluid."

CASE 2.—A 19 year old girl had been ill for two weeks. At death the anatomic diagnosis included acute suppurative lymphadenitis (primary bubo) of the right axilla, acute ependymitis and leptomeningitis, acute degeneration of the kidneys, liver and spleen, chronic fibrous pleurisy and pregnancy of six months. The description of the brain was as follows: "The cerebral leptomeninges contain a slight excess of fluid which appears slightly turbid. On opening the right lateral ventricle, it is found to contain a considerable amount of yellowish-gray pus. The choroid plexus is large and soft. The left choroid is smaller, but also surrounded by grayish exudate. The fourth ventricle is apparently free. The brain substance is pale and shows nothing abnormal."

In both these cases the organisms were cultured from the exudate in the ventricles.

Uriarte [11] observed a patient with iridocyclitis and hypopyon of one eye due to P. pestis. Death occurred suddenly in the third week of illness. At autopsy the meninges were observed to be covered with small abscesses containing the plague bacillus in pure culture. According to Paso,[12] a 39 year old Spaniard suffering from inguinal and submaxillary bubonic-septicemic plague showed signs of meningitis. Despite intensive treatment with antiplague serum (80 to 120 cc.), he died on the fifteenth day, and P. pestis was demonstrated in the turbid spinal fluid.

The most recent report on plague meningitis was made by Montagne and Rivoalen: [13]

An 8 year old child entered the hospital at Dakar, French West Africa, with an axillary bubo on July 8. After the administration of antiplague serum, the enlargement of the node disappeared, but on July 17 nervous symptoms were noted. The Kernig sign was present, there were incessant movements of the hands and eyeballs and spasms of the masseter and left sternocleidomastoid muscle became apparent. The first lumbar puncture and blood culture yielded no organism, while the second puncture, taken on July 20, yielded flaky fluid containing P. pestis. The diagnosis of plague meningitis was confirmed at autopsy on July 21, the thirteenth day after the onset of illness.

The mere demonstration of P. pestis in the spinal fluid at autopsy without gross anatomic changes should not be considered as evidence of plague meningitis. Wu Lien-Teh [14] in a study of 1,921 cases of primary plague pneumonia noted congestion of the meninges and occasional studding of the brain substance with hemorrhages. The spinal fluid was clear, but as a rule positive bacteriologic observations were made.

11. Uriarte, L.: Compt. rend. Soc. de biol. **91**:1039, 1924.

12. Paso, J. R.: Semana méd. **32**:1139, 1925.

13. Montagne, M., and Rivoalen, A.: Bull. Soc. path. exot. **29**:21, 1936.

14. Wu Lien-Teh: A Treatise on Pneumonic Plague, Geneva, 1926, p. 217.

Although the majority of the autopsies that have been reported dealt with patients who succumbed during the acute stage of plague, between the second and the eighth day, it is noteworthy that meningitic involvement was most frequently recorded for patients who survived from the tenth to the twentieth day of the infection. The longest duration of illness was twenty-eight days. In the case under consideration the meningitic localization of the plague process took place in the third week of the disease and persisted in a latent stage for over one hundred days. It is therefore by no means surprising to find a patient in a state of typical plague marasmus, a complication which usually ends in death. This chronic type of plague is claimed to be caused by secondary pyemic infections in which various streptococci and staphylococci play a part. Neither the gross anatomic observations nor the bacteriologic examination of the organs of our patient was suggestive of secondary infection. The marasmus therefore must be attributed to the toxins of the plague bacillus.

Until recently the clinical descriptions have conveyed the impression that plague, with a mortality of from 50 to 75 per cent in the purely bubonic form and of from 75 to 100 per cent solely in the pneumonic form, rarely if ever appears as a chronic infection. The early observation by Choksy [15] and the Austrian Commission,[16] that the plague bacilli may be present in an active state in iliac buboes or in the spleen for forty-eight and fifty-two days, respectively, is rarely mentioned. It is a well known fact that the pus of buboes may contain plague bacilli in an active state one or two months after the onset of the disease (Dujardin-Beaumetz and Joltrain,[17] Léger and Lhuerre [18] and Tanon and Cambessédès [19]). Gotschlich [20] said he isolated the bacilli from the sputum of a patient on the seventy-sixth day of illness, forty-two days after he had risen from his bed. In 1914 Ilvento and Mazzitelli [21] and in 1922 Léger and Baury [22] established the important fact that healthy afebrile persons living in an endemic plague area may harbor virulent P. pestis in small noninflamed lymph nodes. Even more interesting are the reports by Durand and Conseil,[23] who found the bacteria in the

15. Choksy, N. H.: Some Observations on Plague and Its Treatment with Lustig's Serum, Indian M. Rec. **20**:353, 1901; J. Trop. Med. **4**:106, 1901.

16. Footnote 5, p. 532.

17. Dujardin-Beaumetz, E., and Joltrain, E.: Bull. et mém. Soc. méd. d. hôp. de Paris **44**:1739, 1920.

18. Léger, M., and Lhuerre: Bull. Soc. path. exot. **15**:759, 1922.

19. Tanon, L., and Cambessédès: Rev. de méd. et d'hyg. trop. **15**:65, 1923.

20. Gotschlich, E: Ztschr. f. Hyg. u. Infektionskr. **32**:402, 1899.

21. Ilvento, A., and Mazzitelli, M.: Riforma med. **30**:348, 1914.

22. Léger, M., and Baury, A.: Bull. Acad. d. sc. **175**:734, 1922.

23. Durand, P., and Conseil, E.: Arch. Inst. Pasteur de Tunis **16**:92, 1927.

lymph nodes two and twelve months, respectively, after complete recovery or four and fourteen months, respectively, after the onset of the plague. In a more recent article Durand [24] has reported that he isolated the microbes from an inflamed and painful inguinal lymph node seventeen months after the patient had with the aid of antiplague serum recovered from acute bubonic plague.

Influenced by the studies of the French worker, Nikanorow [25] punctured the lymph nodes of 4 healthy persons who had been in intimate contact with plague patients. The axillary nodes of 1 contained virulent plague bacilli.

In view of these reports it is obviously proved that a patient not only in the acute but also in the chronic stage of plague, regardless of the severity of the infection, or an apparently healthy person who has been in contact with the infective agent may be a carrier of virulent plague bacilli for a long time. The history of our patient not only adds another interesting report to the ever increasing series of observations on latent plague but forcibly indicates the progressively important need for studies of sylvatic plague and its relation to man. One cannot escape the impression that the recent cases of plague in the western states merely reflect the behavior of an agent which causes mild infections with a tendency to latency. Nothing is known regarding subclinical infections, yet it is surprising to note that the persons who for nearly twenty years have manned the field investigation laboratories in California and have been continuously exposed to infected fleas and highly infectious rodents have remained absolutely free from plague. When the opportunity arises their susceptibility to P. pestis will be evaluated by cutaneous phagocytic and serologic tests.

Finally, from an epidemiological point of view it may be pertinent to ask these questions: Can a patient with chronic meningeal plague spread the infection? What is the rôle of the human carriers of P. pestis? The French and Russian investigators have maintained that latent bubonic plague may serve as a reservoir and under certain conditions perpetuate the infection by human agency alone. In order to be infective, a patient with latent plague not only must harbor the bacilli in the lymph nodes or the meninges but must also have bacteremia. Durand said he believed that intercurrent infections, such as influenza, measles, etc., may induce a flaring up of the process and that the human flea would then assume the rôle of the vector. At present no evidence has been obtained to support this theory. In fact, there is every reason to believe that, just as in rodents with chronic lesions, in human beings

24. Durand, P.: Arch. Inst. Pasteur de Tunis **20**:77, 1931.

25. Nikanorow, S. M.: Seuchenbekämpfung **4**:140, 1927.

with latent plague the disease ends blindly and breaks the chain of the infection. However, this deduction should not include another frequently drawn conclusion that Pulex irritans may be ignored in the causation of certain outbreaks of plague. The interhuman spread of bubonic plague is a decided possibility, but neither convalescent nor healthy carriers are at all likely to be responsible for the appearance of the disease in the absence of a rodent epizootic. These conclusions guided the public health authorities in permitting the termination of the quarantine measures for our patient and his transference from an infected to a noninfected area.

PHOSPHATASE ACTIVITY, INORGANIC PHOSPHORUS AND CALCIUM OF SERUM IN DISEASE OF LIVER AND BILIARY TRACT

A STUDY OF ONE HUNDRED AND TWENTY-THREE CASES

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An increase in the phosphatase activity of the blood of patients with jaundice was first noted by Roberts [1] in 1930. In a subsequent study of fifty-two cases, Roberts [2] found that the phosphatase level was consistently and markedly elevated in patients with obstructive jaundice, whereas in patients with toxic and catarrhal jaundice the values were only slightly raised or within normal limits. Roberts concluded that by determining the phosphatase activity of the blood, jaundice of the obstructive type could be distinguished readily from toxic, infective and catarrhal jaundice.

Subsequent investigators have confirmed the finding of an increase in the phosphatase activity of the blood in jaundice due to obstruction of the extrahepatic biliary tract, both in patients [3] and in experimental

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A preliminary report appeared in the proceedings of the American Society for Clinical Investigation (J. Clin. Investigation **15**:466, 1936).

1. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930.

2. Roberts, W. M.: Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933.

3. (*a*) Armstrong, A. R.; King, E. J., and Harris, R. I.: Phosphatase in Obstructive Jaundice, Canad. M. A. J. **31**:14, 1934. (*b*) Greene, C. H.; Shattuck, H. F., and Kaplowitz, L.: Phosphatase Content of the Blood Serum in Jaundice, J. Clin. Investigation **13**:1079, 1934. (*c*) Austoni, B., and Coggi, G.: La phosphatase du plasma dans différentes affections, Presse méd. **42**:1594, 1934. (*d*) Herbert, F. K.: The Plasma Phosphatase in the Various Types of Jaundice, Brit. J. Exper. Path. **16**:365, 1935. (*e*) Anderson, R. G.: The Plasma Phosphatase in Jaundice, St. Barth. Hosp. Rep. **68**:221, 1935. (*f*) Fiessinger, N., and Boyer, F.: La phosphatase plasmatique en pathologie hépatique, Rev. méd. chir. mal. du foie **10**:137, 1935. (*g*) Rothman, M. M.; Meranze, D. R., and Meranze, T.: Blood Phosphatase as an Aid in Differential Diagnosis of Jaundice, Am. J. M. Sc. **192**:526, 1936.

animals,[4] and the validity of this observation is generally accepted. In jaundice due to hepatitis, however, the results of determinations of blood phosphatase recorded by different observers vary widely. Bodansky and Jaffe;[5] Greene, Shattuck and Kaplowitz,[3b] and others[6] have found marked increases in the phosphatase activity of the blood in hepatitis so frequently as to invalidate the claim that the determination is of value in differentiating this type of jaundice from jaundice due to obstruction of the common duct. Herbert,[3d] Armstrong, King and Harris[3a] and others,[7] however, have found normal or moderately increased values for blood phosphatase in most cases of hepatitis, high values in such cases occurring only occasionally. These workers have concluded that while the overlapping of values in the several types of jaundice limits the usefulness of the determination in differential diagnosis, the method is nevertheless of value.

These inconsistencies arise, in part, from the use of methods for estimating phosphatase activity that are so different as to preclude a direct comparison of results. (The results, moreover, are expressed in a variety of units.) There are, in fact, difficulties in the way of even a relative comparison of values obtained by Kay's original method with those derived by Bodansky's method, particularly in the higher ranges. In some instances, furthermore, investigators using the same method have reported different values for the range of normal variation,[8] and these differences must be considered when comparisons of the results in cases of jaundice are attempted. Values for phosphatase activity of children and adolescents with catarrhal jaundice[5] have been accepted as markedly elevated, although the values reported are in part below or only moderately above the normal maximum for the respective age groups. It appears, also, that there are important differences in the systems of classification of jaundice employed by various investigators, and it is further apparent that opinions diverge as to the adequacy of evidence necessary for definitely establishing the cause and type of jaundice. There is, finally, the difficulty that while a sharp distinction is drawn between obstructive jaundice and catarrhal jaundice or hepatitis for diagnostic purposes, it is probable that in the latter disorders obstruction also plays a rôle. And, as Herbert[3d] pointed out, varying

4. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: VIII. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, Proc. Soc. Exper. Biol. & Med. **31**:1179, 1934. Armstrong, King and Harris.[3a] Fiessinger and Boyer.[3f]

5. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: IV. Serum Phosphatase of Non-Osseous Origin; Significance of the Variations of Serum Phosphatase in Jaundice, Proc. Soc. Exper. Biol. & Med. **31**:107, 1933.

6. Cantarow, A.: Review of Phosphatase Activity and of Calcium and Electrolyte Metabolism, Internat. Clin. **46**:230, 1936. Fiessinger and Boyer.[3f]

7. Austoni and Coggi.[3c] Anderson.[3e]

8. Greene, Shattuck and Kaplowitz.[3b] Bodansky and Jaffe.[4]

degrees of intrahepatic obstruction may contribute to the diversity of values for phosphatase activity obtained in hepatitis by different investigators.

In view of the interest attaching to the subject, not only with respect to the differential diagnosis but also as regards the mechanism of jaundice, further investigation seems desirable. The observations recorded here were made in twenty-five cases of obstruction of the extrahepatic biliary tract in which the diagnosis was proved at operation or at autopsy; thirty-four cases of jaundice with a clinical course consistent with catarrhal jaundice; thirteen cases of hepatitis due to some known toxic agent; sixteen cases of cirrhosis, proved at autopsy or operation; twenty cases of neoplasm with proved involvement of the liver, and fifteen cases of miscellaneous hepatic disorders.

The results of the determination of the inorganic phosphorus and calcium contents of the serum in these cases are also recorded. The significance of variations from the normal encountered in some cases is considered briefly.

METHODS

Twenty cubic centimeters of venous blood obtained from the patient before breakfast was transferred to a 25 cc. centrifuge tube, allowed to clot for one-half hour and then centrifugated at 1,000 revolutions per minute. Phosphatase activity was determined in duplicate on 1 cc. of serum by Bodansky's[9] method. The results are expressed in Bodansky units, 1 unit being the equivalent of 1 mg. of phosphorus as phosphate ion liberated from a substrate of sodium betaglycerophosphate following incubation for one hour at 37 C. at a p_H of 8.6. When the phosphatase activity exceeded 40 Bodansky units per hundred cubic centimeters of serum, the following positive correction was applied to the result in order to compensate for the inhibiting effect of hydrolytic products following hydrolysis of 10 per cent or more of the substrate.[10]

$$E_1 = E + \frac{E^2}{1{,}000}$$

E represents the original value expressed in Bodansky units and E_1 the corrected value in Bodansky units.

The inorganic phosphorus content of the serum was determined in duplicate on 1 cc. samples by the method of Kuttner and Lichtenstein,[11] with correction for deviations from Beer's law.[12] The calcium content of the serum was determined

9. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93, 1933.

10. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: V. Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, Am. J. Dis. Child. **48**:1268 (Dec.) 1934.

11. Kuttner, T., and Lichtenstein, L.: Estimation of Phosphorus: Molybdic Acid-Stannous Chloride Reagent, J. Biol. Chem. **86**:671, 1930.

12. Bodansky, A.: Phosphatase Studies: I. Determination of Inorganic Phosphate; Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, J. Biol. Chem. **99**:197, 1932.

in duplicate on 2 cc. samples by the Clark and Collip[13] modification of the Kramer and Tisdall method. The bilirubin content of the serum was estimated by the method of Thannhauser and Andersen.[14] The protein content of the serum was determined by difference on 1 cc. samples, the macro-Kjeldahl technic being used for estimating the total nitrogen content, and Folin's method with nesslerization for determining the nonprotein nitrogen content. Albumin and globulin fractions were estimated in duplicate on 0.5 cc. samples by Howe's method, nitrogen being determined by the micro-Kjeldahl technic and titration.

These methods give the following range of variation in our hands: In twenty-five normal adults the phosphatase activity of the serum varied from 1.3 to 3.5 Bodansky units per hundred cubic centimeters, in agreement with the normal range established by Bodansky (1 to 4 units). We have occasionally encountered values slightly in excess of 4 Bodansky units in patients hospitalized for a variety of diseases but without obvious disease of bone or liver. As such slight increases are exceptional and of equivocal significance, we accept 1 to 4 Bodansky units per hundred cubic centimeters as the normal range. Our experience is not in accord with that of Greene, Shattuck and Kaplowitz,[3b] who considered values varying between 2 and 11 Bodansky units per hundred cubic centimeters of serum as without pathologic significance. In children and growing adolescents the phosphatase activity of the serum may be as high as 12 Bodansky units per hundred cubic centimeters.

Normal values for serum calcium range from 9 to 11 mg. per hundred cubic centimeters, and normal values for the inorganic phosphorus of the serum, as determined by the Kuttner and Lichtenstein method, range from 2.5 to 4 mg. per hundred cubic centimeters.

RESULTS AND COMMENTS

Obstruction of the Extrahepatic Biliary Tract.—The phosphatase activity of the serum was found to be definitely increased in all our twenty-five cases of jaundice due to obstruction of the extrahepatic biliary tract (table 1). Preoperative values obtained in twenty-three cases ranged from 37.6 to 12.4 Bodansky units per hundred cubic centimeters. Values of less than 10 Bodansky units per hundred cubic centimeters were obtained in two cases of stone in the common bile duct in which the phosphatase activity of the serum was determined when jaundice was subsiding spontaneously. In case 25 (phosphatase, 4.6 Bodansky units) the patient was not jaundiced when the determination was made, though a stone was found subsequently at operation. In

13. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

14. Thannhauser, J. S., and Andersen, E.: Methodik der quantitativen Bilirubinbestimmung im menschlichen Serum: Ueber die Ehrlich-Pröscher'sche Reaktion, Deutsches Arch. f. klin. Med. **137**:179, 1921.

TABLE 1.—*Summary of Analyses of the Blood in Twenty-Five Cases of Jaundice Due to Obstruction of the Extrahepatic Biliary Tract**

TABLE 1.—*Summary of Analyses of the Blood in Twenty-Five Cases of Jaundice Due to Obstruction of the Extrahepatic Biliary Tract* *

Case No.	Patient	Sex	Age, Years	Cause of Obstruction	Approximate Duration of Jaundice Before Initial Blood Analysis	Urobilin in Stool	Serum: Phosphatase, Bodansky Units per 100 Cc.	Serum: Inorganic Phosphorus, Mg. per 100 Cc.	Serum: Calcium, Mg. per 100 Cc.	Serum: Bilirubin, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Time of Blood Analysis Relative to Operation
1	J. H.	♂	49	Carcinoma of gallbladder	10 days	+	37.6	2.5	9.2	12.5	38	3 days before exploration
2	M. J.	♀	56	Carcinoma of common bile duct	3 weeks	0	35.9	2.6	9.9	19.2	27	2 days before cholecystostomy
							62.1	3.1	...	13.4	26	12 days after operation
3	M. D.	♂	..	Carcinoma of gallbladder	.....	..	28.6	2.6	...	11.4	32	(Autopsy)
4	P. A.	♂	45	Carcinoma of head of pancreas	3 months	0	27.3	3.9	...	7.9	24	2 weeks before exploration
							22.8	2.6	...	6.5	..	1 day before exploration
							21.4	4.9	...	2.8	..	3 days after exploration
5	J. G.	♂	48	Carcinoma of head of pancreas	Many weeks	0	26.8	2.7	...	9.4	29	6 days before cholecystogastrostomy
						0	28.9	2.9	...	8.2	..	2 days before operation
							8.7	2.9	7.8	2.0	22	13 days after operation
6	A. P.	♀	50	Stenosis of common bile duct	5 weeks	+	25.2	2.9	...	10.7	28	1 day before choledochostomy
				Recurrence	23 days	+	34.9	3.0	10.2	7.2	27	3 months later
7	L. W.	♀	42	Carcinoma of body of pancreas	1 day	+	28.7	3.1	9.6	3.9	28	22 days after exploration †
						0	24.2	3.0	...	6.0	..	27 days after exploration
						0	24.0	2.8	8.8	6.3	..	31 days after exploration
						0	34.4	3.1	9.3	9.4	30	41 days after exploration
8	R. C.	♀	54	Stone in common duct	3 weeks	+	21.6	3.3	10.9	4.2	24	8 days before choledochostomy
9	G. R.	♀	41	Carcinoma of head of pancreas	11 weeks	0	21.1	3.1	...	11.7	36	3 weeks before exploration
							23.0	3.0	...	10.2	..	2 weeks before exploration
10	E. W.	♂	54	Stenosis of cholecystogastrostomy ‡	7 days	+	20.2	1.7	8.6	5.5	40	6 months after cholecystogastrostomy
							15.9	4.0	7.5	3.0	52	12 days later
11	D. R.	♂	68	Carcinoma of head of pancreas	14 days	0	19.4	2.2	9.3	10.0	24	1 day before cholecystostomy
							10.6	2.2	9.1	7.1	34	11 days after operation
12	L. R.	♂	46	Carcinoma of common bile duct	6 weeks	0	19.3	2.8	9.5	17.0	37	3 days before choledochostomy
13	K. S.	♀	34	Stone in common duct	.....	+	19.0	3.6	9.6	8.5	26	1 day before choledochostomy
14	M. S.	♀	73	Carcinoma of gallbladder	.....	..	18.6	2.1	8.7	10.5	28	(Autopsy)
15	J. G.	♂	40	Carcinoma of common bile duct	4 weeks	0	18.3	3.2	...	14.4	..	Exploration
16	J. Ha.	♂	56	Carcinoma of head of pancreas	3 weeks	+	17.4	3.8	10.1	5.4	21	1 day before cholecystoduodenostomy
17	R. W.	♀	50	Stone in common duct	5 days	+	14.7	3.4	10.4	3.0	31	1 day before choledochotomy
							10.3	3.8	9.3	1.0	25	12 days after operation
18	R. M.	♂	58	Carcinoma of papilla of Vater	8 weeks	0	14.6	3.0	10.4	14.2	27	6 days before cholecystogastrostomy
							7.3	2.5	8.1	7.5	30	10 days after operation
19	J. P.	♂	48	Stone in common duct	1 month	+	13.8	3.2	10.2	13.7	29	4 days before choledochostomy
20	M. R.	♀	49	Carcinoma of common bile duct; biliary fistula	.....	+	11.0	1.6	8.1	4.5	26	20 days before exploration
21	M. J.	♂	49	Carcinoma of papilla of Vater ‡	3 months	0	13.6	4.0	10.6	10.9	34	8 days before cholecystogastrostomy
							16.8	3.6	...	14.1	..	1 day before operation
							9.4	3.8	...	6.0	..	12 days after operation
							8.5	3.5	...	4.0	27	27 days after operation
				Cholangeitis	5 days	+	21.2	3.0	9.8	3.4	32	10 months after operation
22	J. K.	♂	64	Carcinoma of head of pancreas	Several weeks	0	12.6	2.7	9.7	10.0	28	8 days before cholecystogastrostomy
							15.4	3.6	9.0	10.7	33	1 day before operation
							24.7	2.1	7.4	15.0	29	13 days after operation
							26.6	2.7	8.2	15.0	33	27 days after operation
23	P. K.	♂	41	Carcinoma of head of pancreas	.....	+	12.4	4.7	...	5.8	22	1 day before cholecystostomy
							8.7	2.3	8.0	3.0	26	8 days after operation
							22.7	4.8	9.7	2.0	42	45 days after operation
24	E. M.	♂	73	Stone in the common bile duct	3 weeks	+	6.7	1.3	9.0	7.5	39	6 weeks before autopsy
							...	...	...	2.3	34	5 weeks before autopsy
25	C. C.	♂	51	Stone in the common bile duct	2 weeks	+	4.6	2.9	10.0	1.0	25	5 days before choledochostomy

* The diagnosis was established at operation or at autopsy in every instance.
† Jaundice developed twenty-one days after exploration for carcinoma of the body of the pancreas.
‡ Cholecystogastrostomy was performed at the time of resection of a carcinoma of the common bile duct.

case 24 (phosphatase, 6.7 Bodansky units) jaundice was intermittent. No stones were found in the common bile duct at operation, but some were present at death following recurrence of jaundice.

The values for the bilirubin content of the serum varied widely, from 19.2 to 1 mg. per hundred cubic centimeters. No relation could be made out between the level of the phosphatase activity and the bilirubin content of the serum. The values for the phosphatase activity were not consistently higher in eight cases of complete biliary obstruction than in the remaining cases in which there was incomplete obstruction at the time of examination. There appeared to be no relation between the increase in the phosphatase activity of the serum and the duration of jaundice, so far as this could be ascertained. The highest phosphatase values in this series, however, occurred in cases of carcinoma obstructing the biliary tract, a group in which obstruction is likely to be of long duration and complete. But the claim that obstruction due to carcinoma can be differentiated in this manner from obstruction due to stone [3c] could not be substantiated.

As pointed out by Roberts,[2] the phosphatase content of the blood in obstructive jaundice tends to be relatively high with respect to the bilirubin content of the serum. In our cases the ratio

$$\frac{\text{Serum phosphatase activity (Bodansky units per hundred cubic centimeters)}}{\text{Serum bilirubin (mg. per hundred cubic centimeters)}}$$

was found to exceed 1.0 in all but one instance.

Although no general proportionality obtained between the phosphatase and the bilirubin level of the serum, in six of eight cases studied after the biliary obstruction was relieved surgically the resulting fall in the bilirubin content was associated with a similar but more gradual decline in the phosphatase activity of the serum.

Catarrhal Jaundice; Toxic Hepatitis.—In contrast with the relatively uniform increase in values for the phosphatase activity of the serum obtained in jaundice due to obstruction of the extrahepatic biliary tract, our forty-seven cases of jaundice due to hepatitis (tables 2 and 3) yielded more variable results. In thirty-five instances the phosphatase content of the serum was less than 10 Bodansky units per hundred cubic centimeters. Of the remaining twelve cases of jaundice due to hepatitis, in which values as high as 45 Bodansky units per hundred cubic centimeters were exhibited, it is interesting to note that in six there was a history of exposure to some known toxic agent (toxic hepatitis). And in four of the remaining five cases of catarrhal jaundice analysis of the clinical history revealed complications to which the increased phosphatase content might, in part, be ascribed. In cases 29 and 34 (the patients were 12 and 14 years of age, respectively) the values obtained were within the normal limits for the age groups. One patient (case 27) had had a previous

TABLE 2.—*Summary of Analyses of Blood in Thirty-Four Cases of Jaundice with a Clinical Course Consistent with That of Catarrhal Jaundice or Hepatitis of Unknown Etiology*

Case No.	Patient	Sex	Age, Years	Approximate Duration of Jaundice: Before Blood Analysis, Days	Approximate Duration of Jaundice: Total Duration, Days	Urobilin in Stool	Serum: Phosphatase, Bodansky Units per 100 Cc.	Serum: Inorganic Phosphorus, Mg. per 100 Cc.	Serum: Calcium, Mg. per 100 Cc.	Serum: Bilirubin, Mg. per 100 Cc.	Serum: Nonprotein Nitrogen, Mg. per 100 Cc.
26	B. M.	♀	46	4	35	0	25.3	1.9	7.9	17.7	33
				6		+	24.4	1.6	6.9	11.7	
				16		+	18.5	2.1	9.2	3.0	
				27		+	7.8	2.0	9.4	2.0	26
				35		+	3.3	3.5	9.7	Trace	26
				100		+	2.4	2.8	10.2	0	27
27	D. S.	♂	42	16	5 wks.	+	16.7	1.5	9.8	11.7	21
				31			7.1	4.1	11.0	3.0	
28	E. O.	♂	52	70	3 mos.	+	12.9	3.4	...	6.0	..
				74		+	9.2	5.0	10.9	6.0	26
				96		+	6.8	3.6	...	2.5	27
29	J. S.	♀	12	3	13	0	11.0	4.7	...	8.5	
30	J. C.	♂	22	37	50	+	9.8	3.8	...	6.0	29
31	G. S.	♂	38	3	5	+	9.1	3.1	10.5	2.0	35
				97			5.6	3.1	10.1	2.0	25
32	J. L.	♀	52	9	43	+	9.1	2.3	9.8	20.5	23
				14		+	7.5	3.2	...	18.5	25
33	V.	♀	25	2	14	+	8.9	3.0	10.0	8.4	27
34	S. C.	♀	14	16	42	+	8.9	4.3	10.6	10.5	30
				24		+	7.2	5.5	11.1	6.1	33
				36			11.9	5.4	10.9	7.5	35
35	E. L.	♂	24	14	4 wks.	+	7.7	3.2	10.6	6.3	32
36	A. K.	♂	15	1	2 wks.	0	7.2	3.0	9.7	7.2	34
37	R. L.	♂	23	3	3 wks.	+	6.9	2.8	10.3	6.3	30
38	J. G.	♀	70	14	2 mos.	+	6.0	2.7	10.3	14.4	25
				19		+	10.0	3.0	...	11.2	..
				26		+	7.7	3.3	...	6.0	23
				32		+	6.5	3.3	9.2	3.2	25
				48		+	4.6	3.0	...	2.5	22
39	A. R.	♀	29	15	7 wks.	+	6.7	3.4	10.6	12.5	24
				32			8.7	3.3	...	7.8	
				42			9.4	3.5	10.6	7.7	26
40	M. M.	♂	27	12	19	+	6.7	4.3	9.6	4.5	27
41	D. O.	♂	59	7	22	+	6.7	2.8	8.8	7.4	31
42	A. M.	♀	23	19	45	+	6.6	3.7	...	9.0	25
43	F. M.	♂	6	34	43	+	6.4	4.3	...	1.0	
44	J. T.	♀	23	15	1 mo.	+	6.3	2.9	...	7.3	
45	E. K.	♀	43	5	12	+	6.3	2.8	9.8	5.0	30
				7			5.9	2.6	...	4.3	
46	M. J.	♀	47	8	24	+	5.9	4.0	9.6	18.0	26
47	W. B.	♂	39	15	25	+	5.5	2.9	11.1	10.7	29
48	K. J.	♂	38	15	16	+	5.4	3.5	9.9	2.0	
49	D. G.	♂	23	7	20	+	5.3	4.0	10.6	5.0	29
50	V. G.	♀	56	12	21	+	5.2	4.2	...	7.5	28
				19			3.8	4.2	...	3.3	33
51	P. N.	♂	42	19	31	+	4.6	2.9	9.7	6.7	28
52	F. C.	♂	22	16	30	+	4.5	3.0	11.1	6.3	27
53	C. C.	♀	34	35	43	+	4.1	3.6	10.2	3.8	24
54	D. M.	♀	38	15	6 wks.	+	4.0	2.9	10.0	10.4	25
55	E. F.	♂	40	17	36	+	4.0	2.1	10.2	3.4	28
56	M. R.	♂	22	26	1 mo.+	+	3.9	4.0	....	8.5	26
57	C. W.	♂	37	13	28	0	3.9	3.4	9.5	8.7	
				24		+	2.5	4.6	9.6	Trace	50
58	A. M.	♀	49	11	21	+	3.7	2.6	10.5	4.9	23
59	M. H.	♂	56	17	2 mos.	+	2.9	3.8	....	3.9	33

TABLE 3.—*Summary of Analyses of the Blood in Thirteen Cases of Toxic Hepatitis Following Exposure to Known Toxic Agents*

Case No.	Patient	Sex	Age, Years	Cause of Jaundice	Approximate Duration of Jaundice		Urobilin in Stool	Serum				
					Before Blood Analysis	Total Duration		Phosphatase, Bodansky Units per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.
60	A. S.	♀	22	Arsenical therapy	15 days	1 mo.	+	45.0	3.8	8.9	7.5	22
					18 days		+	37.9	4.4	....	6.9	22
					24 days		+	43.7	4.2	....	4.8	
61	R. S.	♂	37	Arsenical therapy	6 days	35 days	0	24.6	2.7	....	8.3	30
					11 days		+	17.1	2.9	10.7	8.3	27
					30 days		+	10.4	3.8	....	3.0	
62	V. B.	♀	33	Arsenical therapy	17 days	2 mos.	0	15.8	3.0	10.3	11.0	25
63	N. C.	♂	27	Arsenical therapy	20 days	9 wks.	0	12.1	2.7	10.2	11.5	
					31 days		+	6.8	3.6	....	10.0	25
64	C. F.	♂	38	Cinchophen	9 days	27 days	+	12.1	3.7	9.5	8.3	30
65	E. T.	♂	2½	Phosphorus poisoning*	3 days	5 days	+	10.7	0.25	7.1	7.0	
66	M. A.	♂	47	Arsenical therapy	1 mo.	6 wks.	+	8.6	2.9	9.2	6.7	35
67	P. A.	♂	23	Arsenical therapy	16 days	4 wks.	+	7.2	4.2	10.4	8.3	30
68	A. L.	♀	54	Neocinchophen	20 days	34 days	+	7.0	4.7	....	4.0	27
69	D. R.	♂	40	Arsenical therapy	5 wks.	9 wks.	0	6.8	2.0	9.5	13.4	25
					6 wks.		0	6.4	3.6	....	8.0	
70	C. A.	♀	16	Third degree burn*	5 days	6 days	+	5.8	1.2	9.7	31.0	32
71	C. W.	♀	23	Arsenical therapy	25 days	43 days	+	4.9	3.2	10.0	15.3	26
					33 days		+	4.2	2.9	10.5	12.1	
72	D. K.	♂	33	Arsenical therapy	6 days	9 days	+	4.0	2.8	9.6	4.4	33

* The patient died of acute yellow atrophy of the liver several days later. All the other patients recovered.

attack of jaundice six months before and may have had preexistent hepatic damage (see the discussion of the cases of cirrhosis). Another case (case 38) illustrates occasional transient rises in phosphatase activity of the serum during recovery from severe hepatitis.

No relationship between the severity of the jaundice and the height of the phosphatase content of the serum was found in catarrhal jaundice or toxic hepatitis. The ratio of the phosphatase to the bilirubin content of the serum was extremely variable, and even in the presence of intense jaundice and acholic stools there was usually little rise in the phosphatase activity. There was no relation between the phosphatase level of the serum and the duration of jaundice. The phosphatase activity returned to normal as the jaundice subsided.

One of the difficulties encountered in the collection of cases of hepatitis arose from the fact that the exclusion of cases of stone in the common duct, with spontaneous passage, is not always possible. This may be the explanation for some of the high values for phosphatase recorded in cases in which a diagnosis of hepatitis was made. With this possibility in mind, all our patients were followed until the complete disappearance of jaundice, and in many instances roentgenographic examination of the abdomen and examination of the duodenal contents for cholesterol crystals were carried out. We have included only those cases in which no indication of the presence of gallstones was noted.

Our results support the view [15] that the phosphatase activity of the serum in catarrhal jaundice and hepatitis (apart from hepatitis due to toxic drugs) tends to be only moderately increased, marked elevations being exceptions to the rule. It appears that the behavior of the serum phosphatase in catarrhal jaundice or hepatitis usually differs from that in mechanical obstructive jaundice due to stone or carcinoma. It is difficult to reconcile this finding with the view that jaundice in hepatitis is primarily the result of obstruction, whether intrahepatic or due to the presence of a mucous plug in the common duct.[16]

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15. Herbert.[3d] Anderson.[3e]

16. It is the opinion of most investigators that the phosphatase of the serum is elaborated chiefly in the bones, from which it escapes into the blood, whence it passes into the liver and is excreted in the bile. That the bile is rich in phosphatase has been demonstrated repeatedly (Roberts;[2] Armstrong, King and Harris;[3a] Greene, Shattuck and Kaplowitz[3b]). Urine does not contain significant amounts of that phosphatase with which we are concerned here, either in normal (Roberts[2] and Armstrong, King and Harris[3a]) or in jaundiced subjects (Roberts[2] and unpublished data).

The marked increase in serum phosphatase activity regularly observed with obstruction of the excretory channels (bile ducts) is therefore readily explained by the resulting accumulation of phosphatase in the blood. The moderate increase

Of interest also is the relatively high incidence of distinctly elevated values for phosphatase in cases of jaundice which developed after the administration of arsenicals (toxic hepatitis, table 3), as compared with the values in cases of hepatitis of unknown origin.

The presence of chronic hepatic damage preceding the acute attack of jaundice was suspected in some of the patients with hepatitis due to known toxic agents. When preexisting cirrhosis is present, the behavior of the serum phosphatase during an attack of hepatitis may be modified.

Cirrhosis of the Liver.—The phosphatase activity of the serum varied over a wide range in our sixteen cases of cirrhosis of the liver: from 66.7 to 2 Bodansky units per hundred cubic centimeters (table 4). In six cases, the values exceeded 10 Bodansky units per hundred cubic centimeters. No correlation could be made out between the level of phosphatase activity and other changes which occur in cirrhosis. Marked elevations were obtained both in the presence and in the absence of jaundice; and, conversely, in one case (case 84) there was a moderate degree of jaundice without any increase in the phosphatase activity. Nor did a marked elevation appear to be more characteristic of cases of advanced cirrhosis with evidences of portal decompensation.

Autopsy or biopsy of the liver showed Laënnec's cirrhosis in all but four cases in this group (case 73, biliary cirrhosis; case 80, healed subacute yellow atrophy of the liver; case 86, hemachromatosis; case 87, schistosomiasis). The inevitably heterogeneous composition of any group of cases of cirrhosis introduces so many variables that the significance of these variations in the phosphatase activity of the serum remains obscure.

Neoplastic Involvement of the Liver.—The phosphatase activity of the serum was increased in seventeen of twenty cases of neoplasm with proved involvement of the liver, the values ranging from 35.2 to 4.3 Bodansky units per hundred cubic centimeters (table 5). In most instances in which jaundice had not developed, the phosphatase content of the serum was lower than in cases of jaundice, being within normal limits in two cases and only slightly elevated in several others. However, the phosphatase activity may be considerably elevated in cases of

in serum phosphatase activity observed in most cases of hepatitis and the marked elevation in some might well be due to the operation of a partially obstructing factor.[15] But if obstruction is the cause of jaundice in hepatitis, it is difficult to understand why high values (comparable to those found with gross obstruction of the common duct) are not obtained more consistently, particularly in cases of marked bilirubinemia. The subject is discussed more fully elsewhere (Roberts;[2] Armstrong, King and Harris;[3a] Herbert,[3d] and Anderson [3e]).

TABLE 4.—*Summary of Analyses of the Blood in Sixteen Cases of Cirrhosis of the Liver*

TABLE 4.—*Summary of Analyses of the Blood in Sixteen Cases of Cirrhosis of the Liver*

Case No.	Patient	Sex	Age, Years	Basis for Diagnosis	Approximate Duration of Jaundice at Time of Blood Analysis	Urobilin in Stool	Date	Serum							Comment
								Phosphatase, Bodansky Units per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	
73	E. S.	♀	65	Autopsy	.....	+	3/20/36	66.7	1.7	9.4	6.8	29	7.0	...	...	Enlargement of liver; ascites; stone in cystic duct; biliary cirrhosis
						+	5/ 7/36	51.6	1.6	8.5	5.0	24	6.1	3.3	2.8	
						+	6/23/36	45.6	1.9	8.4	5.4	30	5.9	2.7	3.2	
						+	1/ 4/37	31.8	1.5	8.3	...	26	6.4	2.9	3.5	
74	A. B.	♀	43	Autopsy	Not jaundiced	..	1/ 2/34	25.1	4.6	9.7	0	32	...	...	...	Enlargement of liver, ascites and hydrothorax; splenectomy in 1928
							1/22/34	22.5	5.2	....	0	22				
							1/30/34	18.1	4.0	9.3	0					
						+	6/ 6/35	30.3	3.4	8.8	2.0	29	7.9	2.4	5.5	
							11/ 6/35	20.5	3.1	....	Trace	26				
							4/17/36	21.9	3.0	9.2	2.0	27	8.4	2.4	6.0	
75	M. C.	♀	33	Autopsy	Not jaundiced	+	11/19/36	15.1	3.3	9.0	0	22	5.3	2.3	3.0	Hepatosplenomegaly; pancreatitis
76	C. M.	♀	61	Biopsy of liver	5 months	+	10/28/35	13.1	2.7	9.4	2.0	32	7.3	...	...	Hepatosplenomegaly with ascites
					17 months	+	1/25/37	10.8	3.7	7.7	5.0	60	5.7	1.7	4.0	
77	M. S.	♀	53	Autopsy	2 months	+	9/22/36	11.4	2.4	8.5	2.6	22	6.0	2.0	4.0	Hepatosplenomegaly; ascites; syphilis
						+	10/ 6/36	12.0	2.6	8.1	3.0	29	5.4	1.9	3.5	
						+	10/20/36	19.4	3.0	...	3.0	43	6.6	2.0	4.6	
78	A. G.	♂	53	Biopsy of liver	.....	+	11/18/35	10.8	3.1	10.1	4.8	30	...	...	...	Enlargement of liver, not of spleen; no ascites
						+	12/10/35	21.4	4.1	....	3.0	33				
79	E. R.	♂	44	Autopsy	3 weeks	+	7/ 7/36	6.9	2.8	9.7	5.8	36	7.4	1.8	5.6	Enlargement of the liver; purpura
						+	7/ 9/36	3.8	0.7	9.6	8.8	29	7.1	1.7	5.4	
80	J. D.	♂	27	Autopsy	10 weeks	0	5/15/36	5.2	3.3	9.3	8.2	26	7.2	2.2	5.0	Hepatosplenomegaly; ascites; healed subacute atrophy of liver
						+	6/19/36	6.9	2.6	8.6	14.2	23	7.2	1.7	5.5	
81	J. D.	♂	46	Biopsy of liver	3 weeks	+	1/30/36	6.2	3.2	9.8	4.5	32	7.6	3.2	4.4	Hepatosplenomegaly; no ascites; omentopexy 5 years before, when ascites was present
82	M. J.	♂	40	Autopsy	8 weeks	0	10/23/34	5.9	1.8	....	9.1	27	5.7	3.1	2.6	Enlargement of liver, not of spleen; ascites
83	J. H.	♂	54	Biopsy of liver	Not jaundiced	+	12/19/33	4.4	5.6	8.4	Trace	71	5.3	2.8	2.5	Hepatosplenomegaly with ascites
84	E. M.	♀	57	Autopsy	.....	+	6/14/35	3.8	1.9	7.9	9.2	24	4.4	...	...	No enlargement of liver or spleen; no ascites
						+	6/26/35	4.4	2.8	8.3	5.4	22				
85	M. F.	♂	47	Biopsy of liver	Not jaundiced	+	1/ 6/36	3.8	1.4	8.7	1.0	37	6.1	3.2	2.9	Hepatosplenomegaly with ascites
86	J. G.	♂	43	Biopsy of skin	Not jaundiced	+	11/25/35	3.7	3.9	9.4	0	28	6.3	3.5	2.8	Hemachromatosis with enlarged liver; diabetes mellitus; no ascites
87	A. E.	♂	31	Biopsy of liver	Not jaundiced	+	1/30/36	3.6	2.7	9.9	1.0	33	5.7	...	...	Hepatosplenomegaly; no ascites; schistosomiasis
88	A. Z.	♂	58	Biopsy of liver	Not jaundiced	+	12/29/33	2.0	2.5	8.6	0	36	5.7	3.7	2.0	Hepatosplenomegaly with ascites

TABLE 5.—*Summary of Analyses of the Blood in Twenty Cases of Neoplasm with Involvement of the Liver* *

Case No.	Patient	Sex	Age, Years	Primary Tumor	Duration of Jaundice	Serum				
						Phosphatase, Bodansky Units per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.
89	J. J.	♂	52	Carcinoma of tail of pancreas	1 week	35.2	3.8	10.6	4.7	34
90	N. S.	♂	55	Carcinoma of body of pancreas (common bile duct patent)	13 days	24.2	2.3	10.0	6.8	
					14 days	23.7	1.9	....	7.5	43
					19 days	32.7	2.8	....	12.5	
					21 days	26.8	4.0	9.1	14.0	67
91	A. R.	♂	32	Carcinoma of sigmoid flexure	Several months	20.4	2.7	10.1	2.0	31
92	W. M.	♂	42	Carcinoma of urinary bladder	Not jaundiced	20.1	4.2	9.5	0	57
					Not jaundiced	17.7	3.2	9.1	0	45
					Not jaundiced	16.5	3.8	8.6	0	60
93	J. D.	♂	66	Not known	3 weeks	18.1	3.2	10.8	13.6	
94	D. K.	♂	56	Carcinoma of urinary bladder	Not jaundiced	15.8	4.8	9.8	0	62
95	T. P.	♂	41	Carcinoma of rectum	.....	15.5	2.9	....	3.5	
96	M. D.	♀	63	Carcinoma of colon	Not jaundiced	13.8	3.0	....	0	30
97	M. D.	♂	55	Carcinoma of body of pancreas; common bile duct patent	.....	13.7	2.9	....	5.7	34
98	A. C.	♂	52	Primary hemangiosarcoma of liver	.....	9.7	2.3	10.0	2.0	27
99	G. M.	♂	35	Primary carcinoma of liver; portal cirrhosis	2 weeks later	4.6	5.4	8.5	2.0	101
					2 weeks	9.2	2.8	9.2	8.9	22
					3 weeks	8.8	5.4	8.9	12.0	37
100	Y. L.	♀	49	Carcinoma of rectum	Not jaundiced	6.5	2.7			
101	R. M.	♀	47	Carcinoma of body of pancreas (common bile duct patent)	Not jaundiced	6.1	4.2	9.4	0	30
102	N. A.	♀	52	Carcinoma of rectum	Not jaundiced	5.9	3.8	9.4	0	25
103	M. R.	♀	75	Carcinoma of gallbladder	Not jaundiced	5.6	3.2	9.6	0	25
104	R. N.	♀	33	Carcinoma of rectum	Not jaundiced	5.3	4.6	9.8	0	33
105	E. T.	♀	58	Fibrosarcoma of lymph glands	Not jaundiced	4.3	2.5	9.1	0	26
106	W. G.	♂	48	Carcinoma of rectum	Not jaundiced	4.0	2.7	9.4	0	20
107	K. D.	♀	40	Carcinoma of rectum	Not jaundiced	3.9	3.8	10.5	0	24
108	M. G.	♀	80	Lymphosarcoma of lymph glands	1 month	3.4	3.1	8.7	5.8	37

* Hepatic metastases were demonstrated at exploratory operation or at autopsy in every instance.

hepatic metastases without jaundice, as pointed out elsewhere.[17] Values of more than 15 Bodansky units per hundred cubic centimeters were obtained in two cases in which there was no jaundice (cases 92 and 94) included in this series.

An increase in the phosphatase activity of the serum may occur in carcinoma with skeletal metastases, particularly of the osteoplastic type,[18] and this possibility must be borne in mind when one is considering the significance of phosphatase values in cases of neoplasm. In case 92 osteoplastic metastases were present in the spine, ribs and pelvis, and the rise in the phosphatase activity in this case cannot be ascribed solely to the metastases in the liver. In case 94 roentgenographic examination of the skeleton failed to reveal metastases to the bones. An increase in the phosphatase activity was observed in several other cases of carcinoma (not included here) with enlargement and irregularity of the liver, in which exploratory operation or autopsy was not performed.

The fact that in several cases of neoplasm an increase in the phosphatase activity of the serum was the only indication of hepatic metastases—there being no bilirubinemia or clinically obvious hepatic enlargement—led to the hope that the determination might prove useful in the early detection of metastases. Our results suggest that increased values for serum phosphatase occur with more regularity than increased values for serum bilirubin in such cases, but, as table 5 shows, the value for phosphatase may be normal or only equivocally increased in the presence of definite involvement of the liver.

Miscellaneous Cases.—The data for three cases of hemolytic jaundice (cases 109 to 111) are included in table 6. The phosphatase activity of the serum was within normal limits, a result in accord with previous findings.[19] Of exceptional interest are the results obtained for two infants with jaundice due to atresia of the biliary tract. Contrary to expectations, the phosphatase content of the serum was within the normal limits of variation for the age group, despite the obstructive character of the jaundice. The phosphatase activity was definitely ele-

17. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: The Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87 (July 14) 1934.

18. (*a*) Gutman, A. B., and Gutman, E. B.: Paget's Disease: Relative Constancy of Serum Phosphatase Levels Over Periods up to Two Years, Proc. Soc. Exper. Biol. & Med. **33**:150, 1935. (*b*) Gutman, A. B.; Tyson, T. L., and Gutman, E. B.: Serum Calcium, Inorganic Phosphorus and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease of the Bones, Arch. Int. Med. **57**:379 (Feb.) 1936. (*c*) Woodward, H. Q.; Twombly, G. H., and Coley, B. L.: A Study of the Serum Phosphatase in Bone Disease, J. Clin. Investigation **15**:193, 1936.

19. Roberts.[2] Greene, Shattuck and Kaplowitz.[3b] Herbert.[3d] Anderson.[3e]

Hepatic metastases were demonstrated at exploratory operation or at autopsy in every instance.

TABLE 6.—*Summary of Analyses of the Blood in Fifteen Miscellaneous Cases*

Case No.	Patient	Sex	Age	Diagnosis	Duration of Jaundice	Urobilin in Stool	Serum					Comment
							Phosphatase, Bodansky Units per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	
109	B. G.	♂	9 days	Hemolytic jaundice	9 days	+	9.6	10.6	9.5	10.3	30	
110	B. G.	♂	21	Congenital hemolytic jaundice	Many years	+	2.2	5.3	9.5	4.0	48	
111	L. F.	♂	42	Congenital hemolytic jaundice	Many years	+	1.7	2.5	10.3	3.0	37	
112	A. D.	♂	2 mos.	Congenital atresia of bile ducts	7½ weeks	0	11.1	3.2	11.0	10.4	21	Proved at operation
113	L. G.	♂	1 mo.	Congenital atresia of bile ducts	3 weeks	0	6.3	3.7	10.1	12.7	25	Proved at autopsy
114	N. C.	♂	35	Amebic abscess of liver	.....	+	11.8	3.6	....	0	30	Clinical diagnosis
115	S. S.	♂	22	Gaucher's disease of liver and spleen	.....	+	3.1	3.9	10.3	0	29	Proved at operation; biopsy
116	T. S.	♂	74	Hepatitis; Paget's disease	6 days	+	32.0	2.3	....	8.0	25	
						+	28.5	2.5	8.9	2.5	..	2 days later
117	J. B.	♂	57	Hepatitis (?); stone in common duct (?); acute pancreatitis	.....	+	4.1	1.3	....	9.4	..	Amylase in blood, 18 units
						+	10.1	2.9	....	2.9	..	6 days later
						+	25.2	3.0	....	3.0	32	8 days later; 60 units of amylase
						+	19.2	3.3	....	2.3	..	9 days later
						+	10.7	3.0	....	1.5	..	12 days later; 30 units of amylase
						+	2.7	3.4	....	Trace	27	35 days later; 21 units of amylase
118	J. M.	♂	45	Suppurative cholangeitis; carcinoma of hepatic duct; multiple abscesses of liver	4 weeks	+	8.2	2.8	....	19.0	29	
						+	5.9	3.4	....	11.0	..	2 weeks later
119	J. K.	♂	25	Cholecystitis and cholelithiasis; acute pancreatitis	4 days	+	5.5	1.8	9.2	4.3	35	1 day before choledochostomy
							5.5	3.3	9.4	1.0	30	7 days postoperatively
							4.3	3.8	10.3	Trace	33	14 days postoperatively
120	F. B.	♀	28	Cholecystitis	4 days	0	7.3	2.9	9.6	7.5	27	1 day before cholecystostomy
							7.1	3.3	9.1	2.0	36	5 days postoperatively
							8.7	3.8	10.3	2.0	30	16 days postoperatively
121	A .W.	♂	52	Cholecystitis and cholelithiasis	2 days	..	10.4	3.8	9.2	8.8	82	1 day after cholecystostomy
							6.9	1.9	8.2	9.4	67	3 days postoperatively
							9.7	2.5	8.7	4.0	43	10 days postoperatively
							6.5	3.0	8.7	2.0	28	19 days postoperatively
							5.8	1.9	8.2	Trace	29	34 days postoperatively
122	D. S.	♂	38	Cholecystitis	6 days	0	15.6	3.6	....	5.2	29	4 days before cholecystostomy
123	M. O.	♀	75	Cholecystitis and cholelithiasis	3 days	+	14.3	1.9	10.2	8.8	27	1 day before choledochostomy

vated in one case of amebiasis of the liver without jaundice. It seems probable that this elevation was the result of intrahepatic disease. One patient with Gaucher's disease of the liver and spleen (case 115) proved to have normal phosphatase activity. Case 116 further illustrates the necessity for exclusion of certain diseases of bone in the interpretation of values for serum phosphatase for jaundiced patients. In this instance an unexpectedly high value in a case of hepatitis was shown by roentgenograms to be due to the presence of Paget's disease, unsuspected until then. In case 117 jaundice of unknown etiology was complicated by an attack of acute pancreatitis, evidenced by the clinical symptomatology and by a sharp rise in the amylase content of the blood. There was a concomitant transient increase in the phosphatase activity of the serum, whether due to partial obstruction of the common bile duct or of the pancreatic duct could not be determined. In case 118 the condition could not be classified satisfactorily because of uncertainty as to the degree of obstruction caused by a carcinoma of an intrahepatic bile duct at the hilus of the liver.

In the remaining five cases in this group there was a clinical suggestion of obstructive jaundice due to calculi in the common bile duct. Exploratory operation failed to confirm this diagnosis, however, though in all cases there were evidences of cholecystitis and in some cases there was also cholelithiasis (table 6). In these instances the possibility that calculi were present in the common bile duct and became dislodged shortly before operation could not be excluded. The clinical picture could be explained as plausibly, however, by transitory edema of the common bile duct or head of the pancreas or by acute hepatitis complicating inflammation of the gallbladder.

Results of the Determination of the Inorganic Phosphorus and Calcium Contents of the Serum.—The inorganic phosphorus content of the serum was within normal limits in most of the one hundred and twenty-three cases included in this study. In a number of instances, however, the values for inorganic phosphorus were less than the lower limit of normal variation.[20] Hyperphosphatemia was observed in several cases. A satisfactory analysis of the factors affecting the inorganic phosphorus content of the serum in these cases was not possible, but from the data at hand certain inferences regarding the general mechanism involved seem permissible.

20. Although many patients with jaundice were on a diet high in carbohydrate and low in fat, ingestion of dextrose, which causes a fall in the value for serum phosphorus (Harrop, G. A., Jr., and Benedict, E. M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, J. Biol. Chem. **59**:683, 1924), need not be considered as a cause of the hypophosphatemia, as the results recorded here were obtained during fasting.

It was noted that the incidence of hypophosphatemia was highest in cases of cachexia with wasting due to cirrhosis of the liver (table 4) [21] or to carcinoma obstructing the common bile duct (table 1). In a significant proportion of these cases hypophosphatemia was associated with hypocalcemia and was thought to be due to prolonged malnutrition. Impairment of hepatic function may contribute to the fall in the inorganic phosphorus content of the serum, since the incidence of hypophosphatemia in these cases is considerably greater than that observed in cases of carcinoma in general.[22] The marked hypophosphatemia noted in two cases of acute yellow atrophy is further suggestive of this view. In one of these cases (case 65) the inorganic phosphorus content of the serum was by far the lowest in our experience—0.25 mg. per hundred cubic centimeters.

Hyperphosphatemia was associated with definite retention of nitrogen in several cases, and it was ascribed to impairment of renal function. Two patients (cases 29 and 34, table 2) with values over 4 mg. per hundred cubic centimeters were adolescent children, and the results may be regarded as within normal limits.

The calcium content of the serum was within normal limits in most of our cases of hepatitis (tables 2 and 3) and of carcinoma with metastases to the liver (table 5) and in our miscellaneous cases of jaundice (table 6). Moderate hypocalcemia was noted in nine of fifteen cases of cirrhosis of the liver (table 4) and in eight of eighteen cases of carcinoma obstructing the common bile duct (table 1). On analysis of the clinical and chemical findings in the latter groups it became apparent that a number of factors must be considered in any attempt to analyze the mechanisms involved in the development of hypocalcemia in diseases affecting the liver.

Gunther and Greenberg [23] have called attention to the significance of a decreased value for serum albumin in this connection, since a fall in the amount of calcium bound to protein is reflected in the values

21. Labbé and Fabrykant (Le phosphore, Paris, Masson & Cie, 1933) have called attention to lowered values for total phosphorus of the blood in cirrhosis of the liver and have pointed out that the inorganic phosphorus fraction may be decreased. They obtained normal values for a small group of patients with catarrhal jaundice. Fiessinger and Boyer [3f] obtained similar results. Our data do not justify the conclusion [3f] that these two conditions may be differentiated by determining the inorganic phosphorus content of the serum.

22. Jackson, H., Jr., and Taylor, F. H. L.: Calcium, Potassium and Inorganic Phosphate Content of the Serum in Cancer Patients, Am. J. Cancer **19**:379, 1933. Gutman, Tyson and Gutman.[18b]

23. Gunther, L., and Greenberg, D. M.: The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930; The Diffusible Calcium and the Proteins of the Blood Serum in Malignant Diseases, ibid. **46**:67 (July) 1930.

for total serum calcium. The serum proteins were partitioned in eight of our cases of cirrhosis of the liver associated with hypocalcemia. The albumin content of the serum was found to be decreased in every instance, the highest value obtained in this group being 3.7 per cent (table 4). In case 83, however, the fall in the value for serum calcium might be ascribed to hyperphosphatemia and retention of nitrogen.

Hypocalcemia was not present in some cases of cirrhosis of the liver, despite definite decreases in the albumin content of the serum. In several such cases considerable elevation in the value for serum globulin was found, and the maintenance of the level of serum calcium within normal limits might have been effected by an increase in calcium bound to globulin. In view of the prevailing uncertainty as to how much,[24] if any,[25] calcium is bound by serum globulin, particularly in pathologic states, the validity of this explanation remains in doubt. Even large increases in the content of serum globulin did not suffice in some instances to maintain the content of serum calcium within normal limits when the value for serum albumin was markedly decreased.

In many of our cases of cirrhosis of the liver the patient was in an advanced stage of cachexia, so that, in addition to hypoproteinemia due to malnutrition, the effect on the value for serum calcium of protracted deprivation of calcium might be considered. In cases of obstruction of the common bile duct due to carcinoma (table 1) this is an important consideration, since the absorption of calcium is affected adversely by the absence of bile from the gastro-intestinal tract. A further complication was introduced in some cases in this group by the presence of a biliary fistula, either spontaneous (case 20) or operative. As shown experimentally in dogs with biliary fistula,[26] loss of calcium in the bile may result in hypocalcemia. In some of our patients an attempt to avoid the diversion of bile from the body was made by means of cholecystogastrostomy, but the effect of this procedure on the content of serum calcium was not always apparent.

Values for serum calcium of less than 9 mg. per hundred cubic centimeters were obtained in only four of our forty-seven cases of

24. Schmidt, C. L. A., and Greenberg, D. M.: Occurrence, Transport and Regulation of Calcium, Magnesium and Phosphorus in the Animal Organism, Physiol. Rev. **15**:297, 1935. Weir, E. G., and Hastings, A. B.: The Ionization Constants of Calcium Proteinate Determined by the Solubility of Calcium Carbonate, J. Biol. Chem. **114**:397, 1936.

25. Bendien, W. M., and Snapper, I.: Untersuchungen über die Bindung der Kolloide des Serums mit Hilfe von Ultrafiltern erhöhter Durchlässigkeit, Biochem. Ztschr. **260**:105, 1933.

26. Cavazza, F.: Su di alcunde ricerche biochemische nel sangue, nella bile e nel fegato di animali con fistola biliare permanente, Pathologica **27**:241, 1935.

hepatitis. The value for serum calcium was as low as 6.9 mg. per hundred cubic centimeters in one instance (case 26) in which the value for serum protein at the time was 5.7 per cent. No protein partition was carried out. The calcium level of the serum may fall below normal limits in cachectic patients with carcinoma (table 5), as has long been known.[27]

SUMMARY AND CONCLUSIONS

The phosphatase activity, inorganic phosphorus and calcium of the serum were determined in the following cases: twenty-five cases of obstruction of the extrahepatic biliary tract in which the diagnosis was proved at operation or at autopsy; thirty-four cases of jaundice with a clinical course consistent with catarrhal jaundice; thirteen cases of toxic hepatitis due to some known toxic agent; sixteen cases of cirrhosis of the liver, proved either at autopsy or at operation; twenty cases of neoplasm with proved involvement of the liver, and fifteen miscellaneous cases.

The phosphatase activity of the serum was increased in every case of jaundice due to obstruction of the common bile duct, the values exceeding 10 Bodansky units per hundred cubic centimeters in twenty-three of twenty-five instances. The phosphatase activity of the serum was elevated irrespective of the degree or duration of jaundice and whether obstruction was complete or incomplete.

The phosphatase activity of the serum was found to be more variable in catarrhal jaundice or hepatitis, but values of less than 10 Bodansky units per hundred cubic centimeters were obtained in thirty-five of forty-seven cases. The incidence of marked elevation in phosphatase activity was much higher in cases of hepatitis due to known toxic agents than in cases of catarrhal jaundice or hepatitis of unknown cause. Our results support the view that the phosphatase activity of the serum in catarrhal jaundice and hepatitis (apart from hepatitis due to toxic drugs) tends to be only moderately increased, a marked elevation being an exception to the rule.

As values for phosphatase activity which are not definitely elevated tend to rule out jaundice due to obstruction of the common bile duct, the method is useful in the differential diagnosis of jaundice.

The phosphatase activity of the serum varied over a wide range in cirrhosis of the liver. No correlation could be made out with the degree or duration of jaundice or with the stage of the disease.

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27. Gutman, Tyson and Gutman.[18b] Jackson and Taylor.[22] General reviews of the literature on the serum calcium in jaundice are available (Snell, A. M., and Greene, C. H.: The Calcium of the Serum in Jaundice, Am. J. Physiol. **92**:630, 1930. Gray, J. S., and Ivy, A. C.: The Rôle of Serum-Calcium Fractions in the Effect of Viosterol on the Bleeding Tendency in Jaundice, Am. J. Digest. Dis. & Nutrition **2**:368, 1935.)

The phosphatase activity of the serum exceeded the normal limit of variation in most cases of carcinoma with metastases to the liver. The rise in the phosphatase activity is usually definite before the development of jaundice. Since skeletal metastases, particularly of the osteoplastic type, often cause an increase in the phosphatase activity of the serum, their presence must be ruled out.

The phosphatase activity of the serum was within normal limits for the age group in two infants with jaundice due to atresia of the biliary tract. This finding was unexpected, since the jaundice in these cases was of the obstructive type.

The phosphatase activity of the serum was within normal limits in three cases of hemolytic jaundice.

The inorganic phosphorus and calcium contents of the serum were within normal limits in most cases in this series. Hypophosphatemia and hypocalcemia occurred in a significant proportion of these cases, most frequently in cachectic patients with cirrhosis of the liver or with carcinoma obstructing the common bile duct, and also in two cases of acute yellow atrophy. Hypocalcemia in patients with cirrhosis of the liver was usually associated with a decrease in the albumin content of the serum.

CARBOHYDRATE METABOLISM IN EPILEPSY

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In the widespread search for a possible relation between bodily disease and epilepsy, carbohydrate metabolism has been studied by numerous authors. The occurrence of convulsions in states of hypoglycemia either as a result of the injection of insulin or spontaneously in the course of hyperinsulinism has further focused attention on the possible disorders of this function.

One of the difficulties encountered in such a study lies in the absence of indications of dysfunction not primarily related to diabetes. Examinations of large numbers of normal subjects have been made more with the view of determining the character of metabolism not related to diabetes than of evaluating the functions of the organs concerned in carbohydrate metabolism. Therefore, what are described as normal types of curves, with arbitrarily constructed formulas, may be applicable for subjects who are not diabetic or destined to be diabetic, but they do not give any indication of what is occurring when high curves, flat curves or delayed curves are obtained for subjects not prediabetic or diabetic. Yet all these types of curves are designated as normal. Another difficulty is found in the constantly changing standards and in the differences of technic. Much further work is necessary on the function of normal organs under varying conditions before one may do more than compare the results obtained in a group of patients suffering from epilepsy with a group not so afflicted, both being examined under approximately the same conditions.

There has been no uniformity of opinion as to the effect of the type of diet preceding the dextrose tolerance test. Some authors, Sweeney,[1] for example, have stated that no effect is produced on the general curve by a variation of diet. Others, for instance McClellan

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1. Sweeney, J. S.: A Comparison of the Effects of General Diets and of Standardized Diets on Tolerance for Dextrose, Arch. Int. Med. **42**:872 (Dec.) 1928.

and Wardlow,[2] have said that high blood sugar levels are present in patients who received a diet restricted as to carbohydrates before the test; and Kohn, Fries and Felshin [3] found a higher rise and a delayed fall when ketosis had been induced by diet. In most instances dextrose tolerance is determined after oral ingestion. Myers and McKean,[4] among others, have called attention to the effect of variability of time of gastric emptying and of intestinal absorption on the character of the curve for dextrose after oral ingestion. As a consequence, McKean, Myers and Von der Heide [5] have devised a "micro-interval glucose tolerance test," employing intravenous administration.

Others, notably Lennox and Bellinger,[6] have said that there is a close correspondence between the curves obtained after intravenous and those after oral administration. The amount of dextrose administered has varied with different investigators, some using a fixed amount (100 Gm., irrespective of the subject's weight); others, an arbitrary amount (1.75 Gm. per kilogram of body weight), and still others, a fixed larger amount (up to 250 Gm.). Thus, John [7] used a standard amount of 100 Gm. He found a variation in the type of curve for those who were obese and for those who were undernourished. Svensgaard [8] found that in the case of children when 250 Gm. was used, the curves obtained were somewhat higher and more prolonged.

Variation in the technic likewise accounts for some divergence of opinion. Although in many instances the Folin-Wu tungstic acid method is basic, it is known that this is not absolutely accurate, and a true indication of the dextrose tolerance can be obtained only if a method such as that of Somogyi is used. The latter eliminates the nonsugar reducing substances, the readings usually being 15 or 20 mg. per hundred cubic centimeters lower, as demonstrated by Holt and Greisheimer [9]

2. McClellan, N. S., and Wardlow, H. S. H.: Hypoglycemic Reactions Following Glucose Ingestion, J. Clin. Investigation **11**:513, 1932.

3. Kohn, J. L.; Fries, M. E., and Felshin, Gertrude: Spontaneous and Induced Ketosis in Children, Am. J. Dis. Child. **34**:857 (Nov.) 1927.

4. Myers, G. B., and McKean, R. M.: The Oral Glucose Tolerance Test, Am. J. Clin. Path. **5**:299, 1935.

5. McKean, R. M.; Myers, G. B., and Von der Heide, E. C.: Blood Glucose Clearance, Am. J. M. Sc. **189**:702, 1935.

6. Lennox, W. G., and Bellinger, Margaret: Blood Sugar: Comparison of Blood Sugar Curves Following Ingestion and Intravenous Injection of Glucose, Arch. Int. Med. **40**:182 (Aug.) 1927.

7. John, H. J.: A Study of Eleven Hundred Glucose Tolerance Tests, M. J. & Rec. **131**:287, 351 and 398, 1930.

8. Svensgaard, Elizabeth: Blood Sugar in Normal and Sick Children, Acta pædiat. (supp. 4) **12**:1, 1931.

9. Holt, G. W., and Greisheimer, E. M.: "True" Glucose Tolerance in Forty-Two Normal Individuals, Proc. Soc. Exper. Biol. & Med. **28**:547, 1931.

and Campbell, Osgood and Haskins,[10] who showed by a combination of yeast and the tungstic acid method an 11 to 32 mg. lower reading in the former.

There is also a difference in the amount of dextrose present in venous and in capillary blood; Myers and McKean [4] have shown in venous blood that the high peak is usually below 170 mg. per hundred cubic centimeters and that it falls to the level for fasting in two hours, whereas in capillary blood the peak is below 200 mg. per hundred cubic centimeters and falls below 120 mg. in two and one-half hours.

Measurements of the amount of dextrose in the blood after its administration have been made at varying intervals, usually during fasting and one-half, one, two and three hours after the administration. It seems that in the future an additional estimation should be made at the fourth hour. Since most of the investigations have been made in relation to the diagnosis of diabetes, the curves usually have been divided into those for diabetic and those for nondiabetic patients. They are variously described. Mosenthal [11] classified the curves as normal when the rise was between 120 and 160 mg., high when the rise was a peak of 160 mg., prolonged when the curve failed to drop below 120 mg. at the end of the second hour, high prolonged when the curve rose above 160 mg. and failed to return to 120 mg. at the end of the second hour and low when the curve did not rise above 120 mg. John [7] classified the curves into straight (with little or no rise), normal (with a rise to between 160 and 200 mg. but a return to the fasting level in one and one-half hours), prediabetic (with a delay in the return to the fasting level in two and one-half or three and one-half hours) and diabetic (when the return to the fasting level was delayed for from three and one-half to six hours). The consensus is that a normal curve starts at less than 120 mg. at the fasting level, rises to a peak not over 160 mg. and returns in less than two hours to the fasting level. In children it has been found that the return to the fasting level may be delayed for a longer period, two and one-half or three hours. It has been pointed out that overweight children have a lower tolerance for sugar.

The significance, if any, of the variability of the curves in apparently normal subjects is unknown. John found that among 287 subjects of normal weight there were 25.8 per cent with diabetic curves, according to his definition. Therefore, the report of high levels in such conditions

10. Campbell, R. A.; Osgood, E. E., and Haskins, H. D.: Normal Renal Threshold for Dextrose, Arch. Int. Med. **50**:952 (Dec.) 1932.

11. Mosenthal, H. O.: The Interpretation of Sugar Tolerance Tests: The Common Occurrence of Renal Glycosuria, M. Clin. North America **9**:549, 1925.

as dementia praecox (Lorenz [12]) will not be significant until the precise meaning of the term high is understood. High prolonged curves likewise have been found in many diversified conditions of ill health—hyperthyroidism, nephritis, thrombo-angiitis obliterans, carcinoma, epithelioma (Mosenthal), hepatic disease (Gray [13]), acromegaly, melancholia, Parkinson's disease, etc. (Myers and McKean). Large series of these individual conditions must be studied so that when values are found that are higher than those for a large series of normal subjects, the significance may be determined. In this connection it seems that a failure of hepatic homeostasis is responsible for high prolonged curves in experimental animals (Soskin and Mirsky [14]).

Coller and Troost [15] have stated that in hepatic damage the fasting level for sugar is low and the dextrose tolerance curve tends to be of a diabetic type. To the failure of hepatic homeostasis Soskin and Mirsky [14] also attributed the occurrence of hypoglycemic reactions following the ingestion of dextrose. McClellan and Wardlow [2] have described this hypoglycemic reaction as occurring in many conditions—fasting, exhaustion, low renal threshold for dextrose, endocrine and hepatic disease, infections and other miscellaneous disorders. They have noted its tendency when there is only a small rise after the administration of dextrose.

Not only is there a variability of the type of curves in any large material, but individual curves obtained on different occasions show a wide variation in a group of normal subjects; similarly, in those suffering from epilepsy Lennox [16] found that the 20 per cent of high curves obtained at one time was reduced to 10 per cent at a succeeding time. The degree of variability of curves in successive examinations in a group of normal subjects must be further studied.

THE FASTING LEVEL IN EPILEPSY

Wide variations are noted in the amount of sugar in the blood conceived to be within normal limits. This of course is in part due to the methods of examination, the type of diet received preceding the test, the state of general health and other factors perhaps not compara-

12. Lorenz, W. F.: Sugar Tolerance in Dementia Praecox and Other Mental Disorders, Arch. Neurol. & Psychiat. **8**:184 (Aug.) 1922.

13. Gray, Horace: Blood Sugar Standards, Arch. Int. Med. **31**:241 and 259 (Feb.) 1923.

14. Soskin, Samuel, and Mirsky, I. A.: The Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve, Am. J. Physiol. **112**:649, 1935.

15. Coller, F. A., and Troost, F. L.: Glucose Tolerance and Hepatic Damage, Ann. Surg. **90**:781, 1929.

16. Lennox, W. G.: Studies of Metabolism in Epilepsy, Arch. Neurol. & Psychiat. **18**:395 (Sept.) 1927.

ble for all the groups reported on. The consensus is that the uppermost level is 120 mg. per hundred cubic centimeters. Concerning the lowest normal level there is no agreement. Lennox, O'Connor and Bellinger [17] have placed it at 80 mg.; Nielsen,[18] at 75 mg., and Tyson, Otis and Joyce,[19] at 80 mg.

Although an average of 100 mg. per hundred cubic centimeters may be the normal lower level, marked variations occur in supposedly normal subjects to levels below 75 mg. The numbers of such variations in a group must be further determined before any significance can be given to the occurrence of a small percentage of readings below 80 mg. and above a certain minimum.

Lennox, O'Connor and Bellinger, reviewing the literature prior to 1927, showed that an examination of the fasting level for dextrose in the hands of many investigators, usually in a small number of cases, reveals a wide variance of conclusions. Some have called attention to hyperglycemia (Heidema) and some to hypoglycemia (Wladyczko and Josephs). Others found normal values (Kooy, Westen, Holmström, Shaw and Moriarity). Of two authors with a large material, Wuth in 40 patients found a range from 60 to 118 mg., with an average of 90 mg. Weeks, Reimer, Allen and Wishard in 45 patients found values between 46 and 125 mg. Lennox, O'Connor and Bellinger [17] in 2,000 examinations of 267 patients found extremes of 63 and 232 mg., the great majority being between 80 and 120 mg. Fifteen per cent were beyond normal limits, 4 per cent being above 120 mg. and 11 per cent below 80 mg. They concluded that the study failed to show any abnormality in the concentration of sugar in the blood in epilepsy. Felsen [20] in 50 patients found 8 with a sugar content of less than 75 mg. and 6 with a value over 120 mg. per hundred cubic centimeters. Munch-Petersen and Schou [21] in 166 patients found the following fasting levels: 60 to 69 mg. in 5 per cent, 70 to 79 mg. in 26 per cent, 80 to 89 mg. in 45 per cent, 90 to 99 mg. in 22 per cent and 100 mg. in 1 per cent. They used the Hagedorn-Jensen method of examination and did not consider these values as significant.

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17. Lennox, W. G.; O'Connor, Marie, and Bellinger, Margaret: Studies of Metabolism in Epilepsy: II. The Sugar Content of the Blood, Arch. Neurol. & Psychiat. **18**:383 (Sept.) 1927.

18. Nielsen, J. M.: Convulsions of Undetermined Etiology: Studies of the Blood Sugar, Arch. Neurol. & Psychiat. **31**:1055 (May) 1934.

19. Tyson, G. N., Jr.; Otis, L., and Joyce, T. F.: Study of Blood Sugar of Epileptics, Am. J. M. Sc. **190**:164, 1935.

20. Felsen, Joseph: Laboratory Studies in Epilepsy, Arch. Int. Med. **46**:180 (Aug.) 1930.

21. Munch-Petersen, C. J., and Schou, H. I.: Investigations into the Sugar-Metabolism in Epileptics, Especially the Sugar Threshold in Adrenalin- and Glucosis-Hyperglycemia, Acta psychiat. et neurol. **6**:545, 1931.

Nielsen [18] in 58 cases of epilepsy noted a periodic or constant tendency to show a low sugar content, considering the low figure to be 10 per cent below that of normal persons, and he said he thought that a tendency to hypoglycemia is present in about 90 per cent of patients with epilepsy.

Tyson, Otis and Joyce [19] reported that in 56.4 per cent of 92 patients the fasting level was below 80 mg. Haury and Hirschfelder [22] quoted Pigott as stating in a communication before the American Psychiatric Association on May 14, 1935, that a low fasting level for sugar is found in epileptic patients. They examined 25 patients before, during and after seizures and in each case found normal limits before the seizure, in no instance finding hypoglycemia.

In our own material studies in carbohydrate metabolism were carried out on a group of 55 males, ranging in age from 9 to 58 years and in 35 females from 13 to 45 years of age (tables 1 and 2). In 42 males and in 29 females repeated fasting levels were available because both dextrose and insulin tolerance tests were made. The studies were generally made from one to five days apart.

The Randles and Grigg [23] micromethod was used in making the determinations. This procedure is like the usual Folin-Wu method, but only 0.1 cc. of blood is employed. It was carried out on capillary blood obtained from the finger. This method, according to Foster,[24] gives higher and sharper curves for carbohydrate tolerance than does venous blood taken simultaneously. The fact that arterial blood was used is of some value in interpreting the dextrose tolerance curves.

Among the males the fasting level for sugar was found to vary from 52 to 125 mg. per hundred cubic centimeters of blood. The average level was 78.54 mg. and the median 78 mg. In the female patients the levels varied from 55.5 to 102.5 mg., with an average of 79.5 mg. and a median of 80.5 mg. The average level for the entire group was therefore 78.5 mg. and the median 78.8 mg. This is well within the normal range for fasting levels. One must keep in mind that such a figure must be considered as flexible for any given subject, despite the group constancy, provided the subject's level remains within physiologic limits. The reason is seen when an attempt is made to correlate the fasting level on two occasions. Here there is noted a coefficient of correlation

22. Haury, V. G., and Hirschfelder, A. D.: Some Observations upon Blood Glucose in Epilepsy, Proc. Soc. Exper. Biol. & Med. **32**:1658, 1935.

23. Randles, F. S., and Grigg, W. K.: Estimation of Blood Sugar by the Folin-Wu Method, Using One Tenth Cubic Centimeter of Blood, J. A. M. A. **82**:684 (March 1) 1924.

24. Foster, G. L.: Carbohydrate Metabolism, J. Biol. Chem. **55**:291 and 303, 1923.

(r) of 0.27 (Pearson product-moment method). So low a correlation indicates that it is impossible to predict a second reading from a first, even within a day or so, with the patient under constant conditions. This, of course, may explain why different workers have reported

TABLE 1.—*Dextrose Tolerance Tests—Males*

Patient	Age	Weight, Pounds	Dose of Dextrose*	Sugar, Mg. per 100 Cc. of Blood					Comment
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours	
20	9	75.50	+	67.0	104.0	181.0	81.2	125.0	Glycosuria
82	9	63.75	..	86.2	136.0	194.0	94.0	92.0	Glycosuria
80	14	85.00	..	64.4	90.2	64.4	82.5	47.2	
42	14	105.00	..	75.7	97.5	84.0	62.9	77.5	
1	14	.....	..	75.5	135.0	79.0	90.0	78.0	
72	15	148.00	..	83.0	124.0	136.0	121.0	75.8	
45	16	160.00	..	78.8	68.5	79.5	61.0	64.5	
6	16	125.00	..	75.5	124.0	102.0	90.0	79.0	
27	17	101.50	+	69.0	136.0	156.0	75.6	79.0	
86	18	150.00	..	113.0	150.3	169.4	141.0	95.0	
75	18	138.75	+	93.0	112.0	160.0	90.0	79.0	
A	18	116.00	..	73.5	110.0	142.0	45.6	81.0	
85	19	132.00	..	79.3	112.0	88.8	100.0	80.0	
5	20	119.75	+	91.5	125.0	102.0	74.0	80.0	
9	20	147.75	..	62.5	109.0	97.0	92.5	101.0	
32	22	138.00	..	72.0	100.0	108.0	64.0	52.1	
2	23	149.00	..	....	106.0	117.0	71.0	74.0	
6	23	131.00	+	74.5	109.0	83.3	70.9	70.2	
3	24	116.00	..	71.0	159.0	141.0	113.0	98.0	
30	24	128.50	..	79.0	119.0	141.0	111.0	72.0	
15	24	139.03	..	79.0	159.0	153.0	90.0	65.5	
60	25	132.00	+	65.5	108.5	84.0	66.5	111.4	
46	26	146.00	+	95.0	143.0	172.5	115.0	84.0	Glycosuria
88	26	167.00	..	84.3	128.0	95.2	89.7	60.0	
39	27	128.00	..	80.5	112.0	129.0	101.0	95.5	Glycosuria
63	27	121.00	+	76.0	127.0	161.0	115.0	95.0	
74	28	156.00	..	66.0	100.5	99.0	55.0	53.9	
83	29	167.00	..	100.0	143.9	137.0	66.4	65.7	
65	29	118.25	+	79.0	162.0	160.0	103.0	95.0	
51	29	135.50	+	64.0	.....	111.5	107.0	26.0	
84	31	141.75	..	100.0	122.0	.....	165.0	133.0	
17	32	135.00	..	88.0	140.0	117.0	139.0	57.0	
24	34	106.00	+	86.0	139.0	160.0	82.0	102.0	
64	35	168.25	..	85.0	161.0	143.0	85.0	71.0	
40	35	210.00	+	81.0	102.0	86.0	74.0	75.0	
73	36	165.00	+	88.0	106.8	148.5	56.0	89.5	
71	37	177.00	..	61.0	140.0	108.0	80.5	66.3	
61	38	156.00	..	69.2	134.0	146.0	134.0	90.0	
78	39	114.50	..	78.0	102.0	153.0	95.0	79.0	
10	39	126.00	..	72.5	102.1	106.2	79.5	63.4	
67	39	150.75	..	63.0	144.0	135.0	38.0	124.0	
23	40	156.75	..	79.0	128.0	220.0	118.0	123.0	Glycosuria
B	41	107.25	..	68.5	126.0	147.0	137.0	74.4	
69	42	152.50	..	72.0	103.0	94.5	39.0	61.0	
66	43	126.25	..	52.0	102.0	105.0	72.0	44.2	
14	43	220.00	+	88.5	128.0	159.0	127.0	70.5	Glycosuria
8	46	154.25	..	80.6	130.0	144.0	70.3	81.5	
70	47	190.00	+	69.0	166.0	86.0	137.0	82.0	
17	50	134.00	..	77.5	176.0	105.3	76.5	45.5	
22	52	160.25	+	81.0	136.0	154.0	155.0	86.0	Glycosuria
57	54	131.00	..	59.0	81.0	86.0	58.0	42.5	
C	55	133.25	..	83.0	174.0	172.0	122.0	97.0	Glycosuria
25	57	128.50	+	93.0	222.0	204.0	147.0	33.0	Glycosuria
79	58	143.50	..	103.0	246.0	326.0	164.0	119.5	Glycosuria
D	58	125.25	..	98.5	187.0	139.0	33.2	71.9	Glycosuria

* The oral dose of dextrose was 1.75 Gm. per kilogram of body weight except when a + sign is inserted to show that 200 Gm. was given.

widely divergent readings for the fasting levels of patients suffering from epilepsy, although all the levels have fallen within physiologic limits.

It might be predicted from the lack of correlation between two fasting levels for dextrose for the same patient that any attempt to

correlate the fasting level with so constant a factor as the age or the weight would meet with failure as regards a significant *r*. This is apparent from our scatter diagrams. When the correlation of the fasting level for dextrose with the weight is studied, the same failure is observed, whether the patient is underweight, overweight or normal. The outcome is identical if the fasting level is compared with the quotient of the weight divided by the age, the weight being corrected for the height and age according to standard tables prepared for insur-

TABLE 2.—*Dextrose Tolerance Tests—Females*

Patient	Age	Weight, Pounds	Dose of Dextrose*	Sugar, Mg. per 100 Cc. of Blood					Comment
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours	
37	13	118.00	..	72.2	89.0	82.0	72.0	87.0	
49	13	88.25	+	75.0	149.0	118.0	115.0	127.0	Glycosuria
55	14	78.00	+	89.5	252.0	295.0	193.0	156.0	Glycosuria
12	15	104.00	+	98.5	148.0	214.0	191.0	102.0	
48	16	96.75	..	83.5	150.0	141.0	158.0	97.0	Glycosuria
E	16	128.25	..	88.8	135.1	130.0	88.4	82.0	
4	16	130.00	+	83.0	.....	148.0	73.0	114.0	
F	17	100.50	..	74.0	137.0	111.0	92.1	62.5	
87	17	116.00	..	76.0	105.0	105.0	97.0	57.0	
89	17	170.75	..	79.6	149.0	162.0	117.0	84.0	
90	18	115.00	..	78.8	122.2	128.0	82.7	50.0	
38	18	159.00	..	....	154.0	111.0	91.2	74.0	
31	19	90.00	+	72.3	136.2	.....	147.7	31.3	
50	19	116.50	+	72.8	146.5	138.0	77.0	118.0	
49	20	92.50	+	....	184.0	173.0	196.0	.....	Glycosuria
54	21	112.00	..	102.5	110.9	111.0	108.5	85.5	
6	24	110.25	..	80.0	177.0	198.0	132.0	97.0	
43	26	.....	..	83.0	134.0	137.0	78.0	87.5	
29	28	126.50	+	81.0	126.0	102.0	.....	70.0	
41	29	133.00	+	60.5	95.0	.....	52.5	51.0	
53	30	111.50	+	84.0	147.0	118.0	114.3	.....	Glycosuria
36	31	124.00	..	84.5	187.0	151.5	113.3	122.5	
61	32	213.00	..	75.0	211.0	236.0	138.0	105.0	Glycosuria
26	32	101.50	..	84.0	132.0	122.0	113.0	94.0	
56	33	129.50	..	73.0	93.5	101.5	108.5	85.8	
2	33	121.75	..	65.3	90.9	75.4	64.3	47.6	
18	34	125.25	+	83.0	160.0	139.0	96.0	107.0	
21	35	123.00	..	79.0	102.0	49.0	78.5	52.5	
33	37	95.00	+	84.4	86.6	105.0	71.0	56.2	
62	37	113.50	+	83.0	96.0	108.0	98.5	85.5	
42	40	128.00	..	97.0	176.0	147.0	132.0	104.3	Glycosuria
60	41	190.25	+	72.2	137.0	104.0	53.4	103.0	
19	42	191.25	..	85.1	107.0	111.0	83.5	91.0	
58	42	136.25	+	79.4	117.5	145.5	76.5	76.0	
44	45	135.75	+	75.3	136.0	141.0	77.5	68.2	

* The oral dose of dextrose was 1.75 Gm. per kilogram of body weight except when a + sign is inserted to show that 200 Gm. was given.

ance companies. There appears to be no significant correlation. A boy of 9 years might have the same fasting level as a man or woman of 40 or vice versa. The males weighed more than the females—136.4 pounds (62 Kg.) as against 120 pounds (54.5 Kg.) for the median. The males were also somewhat older, 30 to 26.3 years for the averages and 27.5 to 26 years for the medians.

Changes in the amount of dextrose in the blood have been reported as occurring in relation to epileptic seizures. Lennox, O'Connor and Bellinger [17] noted the reports of a number of investigators dealing with small numbers of patients, in various instances stating that the amount

of sugar was low, high or normal before an attack; and they concluded from their study that there was no direct relation between the level for sugar and the seizures. In 3 of 11 patients whose blood was examined immediately after a seizure Felsen [20] found hypoglycemia. Haury and Hirschfelder [22] found a rise in the sugar content during the convulsion proportional to the severity of the attack. In our studies there appeared to be no relation between the fasting level for sugar and the seizures, whether the attacks occurred before or subsequent to the drawing of blood. The fallacy of single readings (to determine a hypoglycemic level) is especially evident in this phase of the study. Thus, readings of 68 and 67.6 mg. per hundred cubic centimeters might be obtained for patients just before an attack, whereas on other occasions, when no attack was imminent, the readings were 83 and 75 mg., respectively. However, wider divergences, as between 65 and 103 mg. and 58 and 87 mg., for two readings were noted for patients who have had no attacks for years. There was no difference in the fasting levels in the cases of organic epilepsy as compared with those of idiopathic epilepsy.

It appears, therefore, that the fasting level in this group of 90 patients falls well within normal limits. It does not vary with age, weight, bromide medication or type of epilepsy. Low levels are seen just before attacks in some patients as frequently as they are seen in others who have not had a seizure for years.

SUGAR TOLERANCE CURVES IN EPILEPSY

Prior to the work of Lennox and Bellinger,[17] only in small series of patients suffering from epilepsy were curves for sugar tolerance reported. They reported on the study of 140 patients. Considering a rise above 160 mg. as high and a rise of less than 120 mg. as low, they found 37 per cent high, 15 per cent low and 48 per cent normal curves. When they analyzed their material, considering a rise to over 165 mg. or a failure to return to 120 mg. at the second hour as high and a rise to not more than 110 mg. as flat, they had 24 per cent high, 6 per cent flat and 70 per cent normal curves. Their data gave no evidence of any abnormality of carbohydrate metabolism that might in itself induce seizures. In relation to the significance of any change in carbohydrate metabolism in epilepsy, Lennox and Cobb [25] said that "a minority of patients show an abnormal or variable response to the administration of glucose, for which the explanation is obscure." Munch-Petersen and Schou [21] found variable curves in their 166 patients but did not think they were significant. In 58 patients Nielsen [18] found 50 who failed to show a rise above 120 mg. and 15 who failed to show

25. Lennox, W. G., and Cobb, S.: Epilepsy from the Standpoint of Physiology and Treatment, Medicine **7**:105, 1928.

a rise above 100 mg. in the first half hour; 39 failed to show a return to the fasting level at the third hour and in 11 the lowest point occurred at the fourth hour. These results are at considerable variance with those reported by others. Tyson, Otis and Joyce [19] in a study of 7 patients found delayed and high curves for 2 patients who had the most frequent attacks.

Dextrose was given orally, one group being given 200 Gm. irrespective of weight and the others 1.75 per kilogram of weight. Blood was drawn from the finger after one-half, one, two and three hours. Specimens of urine were examined for evidence of glycosuria. Ninety patients were studied (tables 1 and 2), the curves being classified as high when showing over 160 mg. per hundred cubic centimeters of blood and low when the acme of the curve did not reach 120 mg. Delayed curves were those that did not fall to at least 120 mg. at the second hour and others that were found to be at a significant point above the fasting level at the third hour. Thus, a curve might be high delayed, i. e., over 160 mg. at

TABLE 3.—*Dextrose Tolerance Curves, Summary*

	High Curves		Low Curves		Normal Curves	
	Number	Percentage	Number	Percentage	Number	Percentage
Males	11	20	13	24	31	56
Females	12	35	7	18	15	47
Totals	23	26	20	21	46	53

the acme and not below 120 mg. at the second hour, or it might be normal delayed. The hypoglycemic phase of the curve was studied, especially in relation to the response of the patient to the administration of insulin.

Twenty-six per cent of the dextrose tolerance curves were high, 53 per cent normal and 21 per cent low (table 3). The highest value noted was 326 and the lowest 80 mg. Statistical correlation of the type of curve to the age, weight, age and weight, sex, and blood pressure were such as to make the coefficient of no value. There was no relationship between the fasting level and the height of the curve or between the lowest level of the insulin tolerance curve and the highest level of the dextrose tolerance curve. Cognizance was taken of the fact that 41 per cent of the patients were underweight. Their weights were corrected in accordance with insurance tables, but the correlation to the highest dextrose value was only 0.218. Only 19 of the entire group were more than 5 per cent overweight, as compared with average values. Of these, only 7 (37 per cent) showed high curves, while 9 showed normal and 3 showed low curves. This is not in keeping with John's figures of 65.6 per cent high curves for obese patients. Only 12 patients were more than 10 per cent overweight, and 4 of these showed high curves.

Thirty-three patients, 17 males and 16 females, were given 200 Gm. of dextrose, irrespective of their weight. Five females and 1 male showed high curves, 3 females and 2 males low curves and 8 females and 13 males normal curves. The 19 per cent high curves for patients given 200 Gm. of dextrose is even lower than the 26 per cent of high curves for the entire group. Giving a patient an overdose of dextrose is in no way a factor in the production of a high curve. This is in keeping with Gray's [13] studies of the comparative responses of patients given varying amounts of dextrose in a tolerance test.

In the age correlations attention may be called to the fact that for the males studied here the high curves were clustered in the group from 50 to 59 years old, while for the females they were in the group from 10 to 19 years old. Since only 1 of these patients had hypertension and none was obese, the reason for this apparently paradoxical distribution must be sought elsewhere. The closest correlating factor seemed to be organic epilepsy. These high curves were seen in 3 of the 7 girls who had organic epilepsy, while 4 others with organic epilepsy showed normal curves. Every high curve for patients 50 years of age or more was seen in a subject with organic epilepsy. However, the cause of the organic change was early senescence, and it is entirely possible that the same disintegrative factors were at work breaking up the hemostatic mechanism for carbohydrate metabolism and producing senescence and epilepsy. This small group of older men was the only one in the present study in which there was a definite age correlation.

As had been noted in the section on the fasting level of the blood sugar, bromide levels of from 75 to 300 mg. per hundred cubic centimeters caused no alteration in the acme of the dextrose tolerance curves.

Some workers have considered curves which fail to return to a level below 120 mg. at the second hour as abnormal. There were 11 patients (12.3 per cent) who showed this type of curve. Four of these showed an acme in the curve below 160 mg. and a return to a normal level by the third hour. Seven were patients who showed peaks over 160 mg., and 4 showed peaks over 215 mg. All but 2 of the patients showed a drop in the curve to a normal level by the third hour, 1 showing a return to 133 mg. and another with a curve reaching 295 mg. showing a return to 156 mg. The latter patient, a girl of 14 years, had been having numerous epileptic attacks just before the test was made. The fasting level was 85 mg. There were no other significant correlative data in these second hour delayed curves. Eighteen patients showed a significant failure for the curve to return at the third hour (20 per cent). Nine were males and 9 females. In 9 of the 18 patients the curve failed to fall below 110 mg. at the third hour, and in 6 cases it failed to fall below 120 mg. This failure to return after three hours was apparently

not related to a high peak, as in 9 patients who showed a third hour delayed curve the peak was high and in 9 it was normal.

In no instance was there diabetes, hyperthyroidism or nephritis, the common causes for high or high delayed curves. Hypertension was noted in only 1 of the 18 patients.

The dextrose tolerance curve for 12 females and 23 males (39 per cent of the patients) dropped below the fasting level. This was not related to the height of the curve (only 6 of the 35 showed high curves; 11 showed low curves). Four of the males had been given 200 Gm. of dextrose, but 12 other males who were given the same dose had no hypoglycemic phase. Nine of the 12 females had been given 200 Gm. This might be significant were it not for the fact that 7 other females who were given 200 Gm. of dextrose showed no hypoglycemic phase. The hypoglycemic phase was not related to any phase of the insulin tolerance curve, the percentage of the return or the returns above the fasting level. The hypoglycemic phase has been reported as occurring in normal persons (Gray and others). Hawk and Bergheim[26] have pointed out that dextrose tolerance studies of (arterial) blood from the finger show curves that are more likely to present a hypoglycemic phase.

The character of the dextrose tolerance curve is not related to the type of epilepsy, organic or functional. An analysis reveals that 39 per cent of the patients with organic epilepsy showed high curves (this of course includes the men over 50), 32 per cent low curves and 35 per cent normal curves.

Finally, the type of curve is unrelated to the result of treatment. Seventy per cent of those with high curves, 63 per cent with low curves and 77 per cent with normal curves were improved on treatment. There is not sufficient difference in the three groups to make the type of dextrose tolerance curve significant as a prognostic measure.

The dextrose tolerance curves in our study may be fractionally analyzed and summarized by comparison with similar analyses of the investigations of others who used the same technic (table 4). Our fasting levels are below those given both for normal and for epileptic subjects and are closest to the figure given by Nielsen.[18] Our one-half hour reading is about that given for normal subjects, except that given by Gray, which is higher and falls between the values given by Nielsen and Lennox for epilepsy. At one hour our reading is a trifle higher than the normal reading and falls between the values in epilepsy, being close to Lennox' figure. At two hours our average is below all the normal levels and again falls between the values given by Nielsen and Lennox for epilepsy. At three hours our values are below the normal levels

26. Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1931.

and slightly above Nielsen's value for epilepsy. The values in the three groups of patients suffering from epilepsy are sufficiently close together to be considered similar. Furthermore, all the values are well within normal zones (charts 1 to 3).

Statistical study of these curves places them closer to normal than any other curves reported for nondiabetic conditions (hypertension without nephritis, renal glycosuria without nephritis, renal glycosuria with

TABLE 4.—*Dextrose Tolerance Tests*

	No. of Subjects	Sugar, Mg. per 100 Cc. of Blood: Average Values	Median Values	Range	Standard Deviation	Coefficient of Variability
Normal Subjects						
Gray						
Fasting	276	96.2	97.8	160-40	19.3	20.0
½ hour	158	149.8	148.1	230-60	31.2	20.8
1 hour	300	126.8	121.2	280-40	37.6	29.8
2 hours	252	111.1	109.5	260-30	30.0	27.0
3 hours	103	97.9	95.0	170-40	21.7	22.2
Lennox						
Fasting	23	102.9	98.6	141-79	14.7	14.4
½ hour	23	140.4	133.7	239-87	33.4	23.2
1 hour	23	122.2	118.3	188-56	34.2	28.0
2 hours	23	115.4	109.3	165-80	20.4	17.6
Nielsen						
Fasting	...	88.0	.....	.....	....	....
½ hour	...	137.0	.....	.....	....	....
1 hour	...	129.0	.....	.....	....	....
2 hours	...	103.0	.....	.....	....	....
3 hours	...	87.0	.....	.....	....	....
Epileptic Patients						
Lennox						
Fasting	139	96.2	95.7	229-68	15.5	16.2
½ hour	137	145.2	145.1	500-83*	29.4	20.2
1 hour	138	136.8	127.9	318-69	42.8	31.2
2 hours	136	117.0	110.5	295-67	34.0	29.0
Nielsen						
Fasting	...	80.0	.....	.....	....	....
½ hour	...	119.0	.....	.....	....	....
1 hour	...	104.0	.....	.....	....	....
2 hours	...	87.0	.....	.....	....	....
3 hours	...	76.0	.....	.....	....	....
Our Results						
Fasting	86	78.5	79.0	52-113	12.2	15.6
½ hour	86	133.8	128.7	68.5-252	34.6	25.0
1 hour	84	134.3	129.0	49-326	42.0	31.2
2 hours	86	97.2	92.0	33.2-196	35.0	36.0
3 hours	85	82.7	81.7	33-156	23.8	28.8

* Statistical computations in this series are based on a range between 240 and 80 mg. Three atypical values between 300 and 500 mg. were omitted in order to represent accurately the more homogeneous measures.

chronic nephritis, nondiabetic pregnancy with a high sugar level, hyperthyroidism, hypothyroidism, hepatic disease, acromegaly, or hyperpituitarism, and hypopituitarism, or dyspituitarism).

THE RENAL THRESHOLD FOR SUGAR

Opinions about the level of the blood sugar at which sugar should appear in the urine are extremely varied. Mosenthal reported 170 mg. per hundred cubic centimeters; Campbell, Osgood and Haskins put it in a range between 125 and 220 mg., while John found that glycosuria

occurs at levels below 180 mg. of dextrose in the blood in 83.8 per cent of normal subjects. He has called attention to an individual threshold for each person. In some cases no glycosuria occurred when the amount of dextrose in the blood was over 200 mg. per hundred cubic centimeters. In from 16 to 20 per cent of the normal subjects in whom it occurred there was over 180 mg. of dextrose per hundred cubic centimeters of blood, as well as in 20 per cent of the underweight and 46 per cent of the obese subjects.

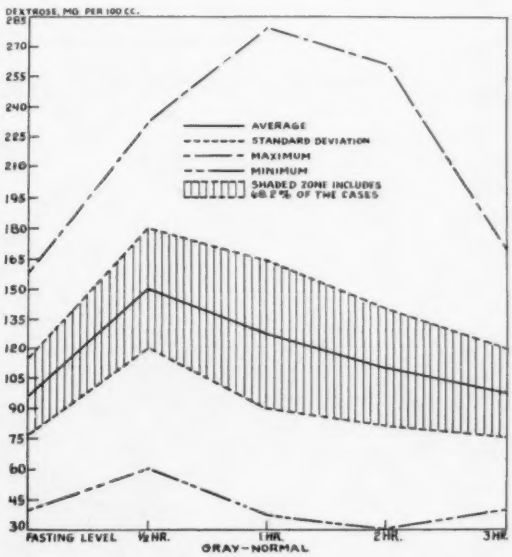

Chart 1.—Dextrose tolerance curves for normal subjects reported on by Gray. The shaded zone indicates the normal values.

Lennox and Bellinger, from 209 observations on 140 patients, found glycosuria in 32 per cent. At the end of the second hour in 64 per cent there was glycosuria when the value for blood sugar was over 200 mg., in 50 per cent when it was between 175 and 199 mg., 21 per cent when it was between 150 and 174 mg., 28 per cent when it was between 125 and 149 mg. and 10 per cent when it was below 125 mg. Felsen, not measuring the amount of sugar in the blood, noted that after the ingestion of 200 Gm. of dextrose only 15 of 47 patients excreted sugar in the urine at the end of the second hour. He concluded from this that epileptic patients can tolerate and store large amounts of carbohydrate. Munch-Petersen and Schou in a study of 36 patients found no sugar in the urine of 9 when the blood sugar content was about 180 mg., of 7 when it was below

160 mg. and of 2 when it was above 250 mg. Since they combined injections of epinephrine and of dextrose, the results are not comparable with those given in other reports.

Of 90 patients with hyperglycemia induced by the oral administration of dextrose, only 18 showed glycosuria, 11 males and 7 females (20 per cent). Most of the patients who showed urinary sugar had attained a high level of dextrose tolerance, although sugar was present in the urine of patients with levels as low as 129 mg. for blood sugar.

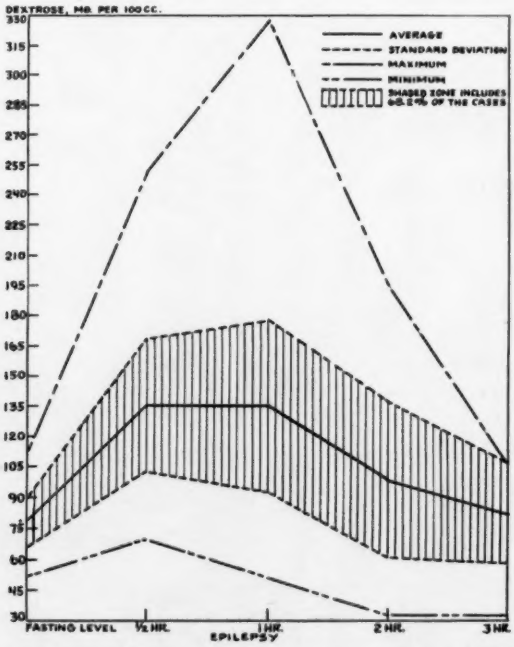

Chart 2.—Dextrose tolerance curves for our series of epileptic patients.

Eleven of the 18 patients showed high curves, i. e., over 160 mg., and 3 did not fall below 120 mg. at the second hour (so-called diabetic type of curve). On the whole, the normal thresholds were high, 189 mg. for the females and 187 mg. for the males, an average of 188 mg. for the group. However, as has been pointed out by many authors, individual analyses do not follow group figures. Thus one sees an occasional level as high as 290 mg. unaccompanied with dextrose in the urine. The ranges given by John for normal subjects show an average of above 140 mg. and below 180 mg. observed in 83.8 per cent of the patients. Only 9 (69.2 per cent) of 13 of our patients with over 180 mg. of

sugar in the blood had glycosuria. If the normal threshold is considered as 160 to 180 mg. (Hawk and Bergheim [26]), 14 patients showed an increased tolerance. However, individual variations forbid the stressing of this point.

Of more significance is the fact that there are no evidences of a decreased tolerance, i. e., glycosuria with a low content of blood sugar, as in "renal diabetes."

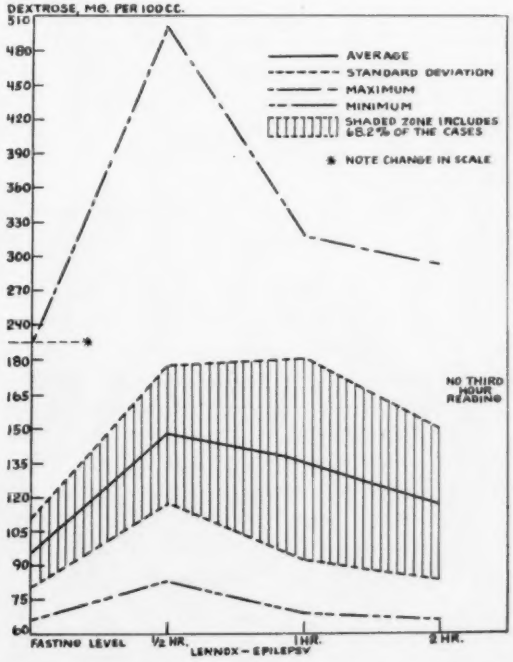

Chart 3.—Dextrose tolerance curves for the epileptic patients reported on by Lennox.

INSULIN TOLERANCE TESTS

Analogous to the increase of sugar in the blood after the administration of dextrose is its diminution after the injection of insulin. After the injection of insulin the amount of sugar in the blood diminishes at a certain rate, then increases at a certain rate to the fasting level. The insulin has been injected intravenously and intramuscularly. It has been given in certain stated amounts, as 10 units, irrespective of the subject's weight, and in certain amounts representing 0.1 unit per kilogram of body weight. As with tests for sugar tolerance, so with those for insulin tolerance—there seems to be a marked variability in

the response of normal subjects, and the complete significance of certain deviations is not known.

McCormick, MacLeod, Noble and O'Brien [27] have said that the extent of the reduction of the sugar content does not follow closely the dose per kilogram or correspond to the actual level of the blood sugar before the injection is given. Neither does the method of injection, intramuscular or intravenous, make any significant change in the steepness of the curve. The subsequent behavior depends partly on the dose of insulin and partly on the glycogen content of the liver. Sevringhaus, Kirk and Heath [28] examined 8 students, 4 units of insulin being given to 4, 8 to 2 and 10 to 2. They found that the types of curves varied and were unrelated to the dose per kilogram of body weight. The duration likewise was variable, and the symptoms of hyperinsulinism appeared at no definite level. Roughly, the extent and duration seemed parallel to the dose.

Bodansky and Simpson [29] examined men after the intravenous injection of 2 units of insulin and found that the lowest level occurred about eighteen minutes after the administration. The total depression they considered as related to the weight, and the depression was slower in fat persons. The return began immediately after the lowest point was reached and was complete in seventy-five minutes, being delayed in those who were overweight. This relation to weight has been observed by others. For example, when 10 units of insulin was injected subcutaneously, it was observed that in obese persons the average fall was 28 mg., whereas in undernourished subjects it was 59 mg. Collens and Grayzell,[30] injecting 0.2 unit per kilogram of body weight intravenously, found the lowest sugar level at the end of the first half-hour and a rapid recovery to the fasting level within forty-five minutes. Better to study the type of curve, Sendrail [31] computed the area enclosed by joining with the base line the points of the sugar levels during fasting, one-half hour and at other intervals, and in this way obtained an indication of the depth in fall and the slowness of the return as reflected by differences in the areas. In addition, he noted in 16 normal sub-

27. McCormick, N. A.; MacLeod, J. J. R.; Noble, E. C., and O'Brien, K.: The Influence of the Nutritional Condition of the Animal on the Hypoglycemia Produced by Insulin, J. Physiol. **57**:234, 1923.

28. Sevringhaus, E. L.; Kirk, Elizabeth, and Heath, H. J.: The Duration and Magnitude of the Hypoglycemia After Insulin, Am. J. M. Sc. **166**:677, 1923.

29. Bodansky, Aaron, and Simpson, Sutherland: Blood Sugar of Normal Human Subjects After the Intravenous Injection of Insulin, Quart. J. Exper. Physiol. **17**:57, 1927.

30. Collens, W. S., and Grayzell, H. G.: Blood Sugar Response to Intravenous Insulin in Normals and in Diabetics, Proc. Soc. Exper. Biol. & Med. **28**:487, 1931.

31. Sendrail, M.: L'épreuve de tolérance à l'insuline, Ann. de méd. **27**:289, 1930.

jects that the drop in the amount of sugar averaged 24 mg. and that the return to the fasting level occurred within an average of sixty-five minutes and never with an interval of over ninety minutes.

Although variations occur, the expected curve is one in which the greatest fall is noted within the first half-hour when the insulin is given intravenously or in large amounts subcutaneously, and probably it is the same when doses of 10 units are given subcutaneously. The return begins promptly and is complete in less than three hours, usually within thirty-five minutes, the average interval being sixty-five minutes. Increased sensitivity, reflected by a greater fall than is expected in the normal subject, has been observed in diabetic patients and in animals with an Eck fistula (Sprague [32]). In animals like rats a return to a level below the original fasting level has been observed after the third hour. This may persist for as long as six hours and has been explained on the basis of inanition (Hrubetz [33]).

The percentage of normal subjects in whom the fall exceeds the arbitrary figure of 30 mg. per hundred cubic centimeters must be ascertained. In some instances after a standard dose of 10 units of insulin, a fall of from 9 to 45 mg. has been recorded in normal subjects and as high as from 42 to 62 mg. in undernourished subjects. The delay in fall, the delay in return and the failure of return also must be carefully studied in a large number of normal subjects. For the most part one can only record the findings for a group of patients with epilepsy and guess at the general resemblance to expected normal curves.

Baudouin and Azérad [34] examined 19 patients with epilepsy, injecting 10 units of insulin intravenously. They recorded an expected fall in the first half-hour in 16 of the patients, and all showed a return nearly to the fasting level by the third hour. In 4 the sugar content of the blood dropped below 30 mg., in 1 to 16 mg.

In an article which appeared after our study had been completed, Ziskind and Bolton [35] reported on insulin tolerance tests on 40 patients with epilepsy. In 20 patients trauma, syphilis, encephalitis, alcoholism, psychoneuroses, narcolepsy or an "organic condition" was thought either to be the cause of the convulsive disorder or to be associated with it. The major thesis of their experiment was to determine the effect of induced hypoglycemia on the convulsions. They gave from 10 to

32. Sprague, Randall G.: Effect of "Chronic" Experimental Liver Damage on the Blood Sugar Response to Insulin, Am. J. Physiol. **110**:488, 1934.

33. Hrubetz, M. Caroline: The Time Curve After Insulin, Am. J. Physiol. **110**:384, 1934.

34. Baudouin, A.; Azérad, E., and Lewin, J.: Epreuve d'hypoglycémie insulinique chez les épileptiques, Compt. rend. Soc. de biol. **114**:902, 1933.

35. Ziskind, Eugene, and Bolton, Ruth: Insulin Hypoglycemia in Epilepsy, Arch. Neurol. & Psychiat. **36**:331 (Aug.) 1936.

60 units of insulin subcutaneously to the 40 patients, and in no instance did a convulsion ensue, although in 1 instance the sugar content of the blood dropped to 28 mg. per hundred cubic centimeters.

The fact that the doses of insulin, varying from 10 to 60 units, were so much greater than those used by us in all but 5 cases, precludes any comparison of the curves. However, a failure for the curve to

TABLE 5.—*Insulin Tolerance Tests—Males*

Patient	Age	Weight, Pounds	Units of Insulin	Sugar, Mg. per 100 Cc. of Blood				
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours
20	9	75.50	10	73.5	47.0	78.0	90.5	88.0
82	9	60.75	10	109.0	77.0	62.2	64.0	55.0
11	11	.....	10	80.0	....	50.2	37.8	48.1
28	14	93.00	10	92.0	68.5	41.5	91.0	80.5
80	14	85.25	10	54.5	60.4	37.9	21.9	33.1
42	14	105.00	10	73.0	50.7	51.5	58.8	59.0
72	15	148.00	10	73.5	67.0	60.0	67.0	80.0
45	16	160.00	10	94.0	62.7	51.5	74.0	77.0
11	16	118.00	10	80.0	76.6	46.5	57.8	60.0
86	18	150.00	10	125.0	94.3	65.7	67.4	82.0
75	18	138.75	10	93.5	77.0	82.0	75.0	94.0
A	18	116.00	10	71.0	40.0	40.5	34.2	37.2
85	19	132.00	10	64.8	42.3	54.0	49.5	64.5
5	20	119.75	10	70.5	70.5	48.0	60.0	64.5
32	22	138.00	10	73.0	38.0	36.0	46.0	61.0
6	23	131.00	10	82.0	75.0	37.5	53.5	67.2
46	26	146.00	10	78.4	49.2	53.2	60.6	74.2
88	26	167.00	10	67.6	36.0	Too low	52.6	66.0
39	27	128.00	10	76.2	49.8	35.1	47.2	46.2
63	27	121.00	10	73.0	60.0	49.0	56.6	66.8
74	28	156.00	10	66.0	55.2	38.5	43.0	49.5
65	29	118.25	10	80.5	47.1	41.6	47.6	63.5
84	31	141.75	10	86.8	57.4	32.8	46.0	56.1
64	35	168.25	10	86.0	64.0	61.0	71.0	56.0
73	36	165.00	10	87.0	76.0	96.0	81.0	51.0
71	37	177.00	10	67.0	58.0	30.9	51.2	50.9
61	38	156.00	10	115.0	74.0	79.0	53.0	80.0
78	39	114.50	10	79.5	69.5	44.0	51.0	44.0
10	39	126.00	10	77.4	62.1	22.5	25.0	26.3
5	39	150.75	10	78.0	50.0	40.0	31.0	35.0
68	39	153.00	10	78.0	68.0	63.0	38.0	53.0
69	42	152.50	10	52.6	34.6	34.8	40.2	42.7
66	43	126.25	10	68.0	39.0	35.4	42.7	41.8
8	46	154.25	10	108.0	83.5	68.2	54.5	76.0
70	47	190.00	10	70.5	39.0	47.0	51.5	55.3
77	50	134.00	10	97.0	78.0	38.0	43.3	51.8
57	54	131.00	10	86.6	59.0	37.5	24.5	17.0
C	55	133.25	10	71.0	75.0	62.0	47.5	39.5
25	57	128.50	10	79.5	89.0	41.5	43.2	51.3
79	58	143.50	10	96.0	86.5	64.5	43.5	56.0
D	58	125.25	10	101.0	79.3	40.3	62.3	73.0

return to the fasting level at the end of the third hour was seen in 28 of the 29 patients for whom the fasting level was recorded in their table.

Insulin tolerance tests were performed on 70 of the patients with epilepsy, 41 males and 29 females, who were included in our dextrose tolerance studies (tables 5 and 6). Each was given 10 units of insulin subcutaneously, regardless of the body weight, except 9 females, who were given 0.1 unit per kilogram of body weight. While the general response of these 9 females was similar to that of the rest of the group, certain differences will be worth pointing out later in the detailed description.

All but 5 of the 70 patients showed a fall within one-half hour after the administration of insulin. These 5 showed a reduction in the sugar level at the first hour, but 3 showed little or no return at three hours, 1 a poor return and 1 a fairly good return. The last patient showed the same level at one-half hour as during fasting. The other 4 showed a rise one-half hour after the administration of insulin. The curves for these 5 did not differ in depth from those for the others.

While it seems from the literature that the lowest level should be attained within one-half hour and the return to near-fasting levels within ninety minutes, our studies do not bear this out. Of the 70

TABLE 6.—*Insulin Tolerance Tests—Females*

Patient	Age	Weight, Pounds	Units of Insulin	Sugar, Mg. per 100 Cc. of Blood				
				Fasting	½ Hour	1 Hour	2 Hours	3 Hours
37	13	118.00	5.3	84.0	32.8	68.5	83.0	72.6
55	14	78.00	10.0	85.5	63.4	40.0	52.3	64.0
12	15	104.00	10.0	73.5	68.5	35.0	22.0	29.6
48	16	96.75	4.4	69.0	72.8	59.7	63.2	66.6
E	16	128.25	10.0	66.5	54.5	33.8	39.2	52.5
4	16	130.00	10.0	87.0	57.5	49.0	65.5	94.0
F	17	100.50	4.6	90.0	37.0	43.0	36.0	52.0
87	17	116.00	10.0	74.6	66.1	31.0	46.5	55.0
89	17	170.75	10.0	77.2	61.3	56.7	45.0	48.0
90	18	115.00	10.0	84.0	76.2	76.7	50.0	54.0
38	18	159.00	7.1	89.0	43.5	50.0	72.6	81.5
31	19	90.00	10.0	75.4	45.4	30.7	44.3	62.0
59	19	116.50	10.0	96.0	65.8	57.4	57.2	56.5
49	20	92.50	10.0	77.5	....	51.0	58.0	57.0
54	21	112.00	5.9	72.9	29.7	42.5	69.0	78.0
G	24	110.25	10.0	91.8	49.5	38.2	52.6	52.6
36	31	124.00	5.6	73.5	33.0	65.0	77.5	70.0
61	32	213.00	9.7	72.0	32.0	58.2	71.6	76.0
26	32	101.50	4.6	70.5	....	66.0	76.0	82.5
56	33	129.50	10.0	81.5	66.0	39.2	48.8	48.8
2	33	121.75	10.0	55.5	39.3	32.6	32.8	31.7
16	34	125.25	10.0	66.5	58.2	38.8	48.2	52.6
21	35	123.00	10.0	73.0	48.3	53.8	80.0	66.0
33	37	95.00	10.0	79.0	68.0	44.2	59.0	76.5
42	40	128.00	5.8	89.0	41.6	81.0	74.1	78.2
60	41	190.25	10.0	76.0	64.5	67.0	76.5	50.2
19	42	191.25	10.0	83.0	22.5	44.5	81.4	89.0
58	42	136.25	10.0	82.5	78.0	60.2	52.0	50.0
44	45	135.75	10.0	92.0	76.0	62.5	43.0	46.5

curves only 18.6 per cent were at the lowest point at the one-half hour reading; 47.1 per cent were lowest at one hour, 21.4 per cent at two hours and 13.0 per cent at three hours. It is possible that this larger dose given subcutaneously produces a slower but more prolonged action than the intravenous dose usually described.

The average fall in the group of patients who were given 10 units of insulin was 41.8 mg. per hundred cubic centimeters, while that in the 9 who were given 0.1 unit per kilogram of body weight was 41.4 mg. The drop may therefore be related more to the method of administration and the metabolism of the patient than to the size of the dose (Sevringhaus, Kirk and Heath [28]).

Weight correlations were made because several reports have been made regarding a difference in the falls in underweight, overweight and normal subjects. The average fall was 44.5 mg. per hundred cubic

centimeters for the overweight females in our group, 45 mg. for the females of normal weight, 31.6 mg. for the females who were underweight, 40.6 mg. for the males who were overweight, 44.6 mg. for the males of normal weight and 44.3 mg. for the males who were underweight. This is in contrast to other figures which have shown that the sugar levels for undernourished subjects fall farther than those for normal subjects who are receiving insulin.

Fifty per cent of all the curves fell over 40 mg. per hundred cubic centimeters, 41 per cent fell from 40 to 20 mg. and only 9 per cent fell less than 20 mg. (table 7). In distinct contrast to the results reported in the literature which lead one to expect a return to fasting or almost

TABLE 7.—*Insulin Tolerance Curves; Summary*

	Drop Phase of Curve for Blood Sugar						Return Phase of Curve for Blood Sugar					
	Less Than 20 Mg.		20 to 40 Mg.		Over 40 Mg.		Over 50%		Under 50%		No Return	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Males	3	7	20	40	18	44	19	46	16	39	6	15
Females	3	11	9	31	17	58	18	62	8	28	3	10
Totals	6	9	29	41	35	50	37	53	24	34	9	13

TABLE 8.—*Summary of Insulin Tolerance Tests for Our Epileptic Patients*

	Number of Patients	Sugar per 100 Cc. of Blood			Standard Deviation	Coefficient of Variability
		Average Values	Median Values	Range in Values		
Fasting	71	80.5	83.2	52.6-125.0	13.0	16.2
½ hour	66	57.7	60.6	29.7- 94.0	16.5	28.6
1 hour	70	52.6	48.7	22.8- 93.0	16.6	31.6
2 hours	70	55.4	53.5	21.9- 90.5	16.9	30.6
3 hours	70	60.3	58.6	17.0- 89.0	16.7	27.8

fasting levels in ninety minutes, only 21 per cent of the 70 patients showed a 90 per cent or better return at three hours. A return of over 100 per cent was noted for 11.4 per cent, and 13 per cent did not show a return at all. Only 53 per cent returned beyond 50 per cent.

The entire picture of the insulin tolerance curve of the 70 patients is evident in an analysis of the median at each reading. From a fasting level of 83.2 mg. per hundred cubic centimeters, the curve of the median drops to 60.6 mg. at one-half hour and to 48.7 mg. at the first hour; it returns to 53.5 mg. at the second hour and to 58.6 mg. at the third hour—24.6 mg. below the fasting level. The last represents a 28.7 per cent failure to return (table 8).

Studies of the averages which we obtained indicate that there is a fasting level of 80.5 mg. per hundred cubic centimeters, with a drop to 57.7 mg. at one-half hour, to 52.6 mg. at one hour, to 55.4 mg. at the second hour and to 60.3 mg. at the third hour—a 63 per cent return.

It is significant that no matter how the figures are analyzed, the greatest fall is at the first hour and the return is incomplete. When an attempt is made to correlate the low point of the curve for insulin or the return with the age, weight, state of nutrition and height or with the dextrose tolerance curve, so low a coefficient is obtained that it is evident that at least in this group no relation exists. There is no correlation between the highest sugar level after the administration of dextrose and the lowest level after the injection of insulin, or between the percentage return of the former and the percentage recovery of the latter. Nothing in the configuration of the dextrose curve is related to that of the insulin curve; e. g., in patients who show a late fall in the dextrose curve below the fasting level, no rise above the fasting level occurs late in the insulin curve.

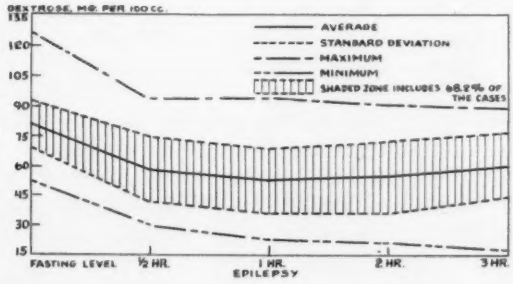

Chart 4.—Insulin tolerance curves for our series of epileptic patients.

The average low point for the group was 41 mg. per hundred cubic centimeters, both males and females showing a similar figure. The median of the low readings for males was 40 mg. and that for females was 40 mg.; therefore, the same reading holds for the entire group. For the patients with organic epilepsy the figures ran somewhat lower, 37 mg. being the average for the males and 33.5 mg for the females, making the average for the entire group 36.4 mg. The median was 39 mg. for the males, 33.5 mg. for the females and 39 mg. for the entire group. The average fall for the males with organic epilepsy was 45.5 mg., for the females 49.5 mg. and for the entire organic group 46.5 mg. This was higher than that for the entire group, which showed somewhat lower values—42 mg. for the males, 39 mg. for the females and 40.6 mg for the entire group (chart 4).

While patients who responded well to treatment showed a drop in the insulin tolerance curve to very low levels (20 mg.), others showed a lack of response. There were 4 such patients. Two showed a cessation of seizures over a period of about eighteen months, while in 2 others the seizures occurred as before. All other attempts to utilize

the insulin tolerance curve or any part of it as a clue to whether or not a patient would do well met with failure. Nothing in the insulin tolerance curve, as in the case of the dextrose tolerance curve, could be used as a prognostic index.

HYPOGLYCEMIA AND THE CONVULSION IN EPILEPSY

The observation of convulsions resulting from a decrease in the sugar content of the blood after an injection of insulin and the discovery of cases of hyperinsulinism with convulsions, due to tumors in the pancreas, led to the assumption that the hypoglycemic state can precipitate convulsions in epilepsy. Harris [36] has stated that in more and more cases convulsive disorders will be found to be manifestations of hypoglycemia. Griffith [37] found low values for blood sugar for patients with convulsions and drew a similar inference.

As stated previously, Baudouin and Azérad, despite the marked hypoglycemia produced in some cases, said they were unable to produce either convulsions or attacks of petit mal by the injection of insulin in epileptic patients.

One must keep in mind that the lower the dextrose reading is below about 60 mg. per hundred cubic centimeters, the greater the error in the measurement. The blue color becomes so faint that it is hard to match it even with comparable known standards. Yet when readings are down in this questionable zone, they emphasize the fact that these patients are in a hypoglycemic state.

Fifty-five of our 70 patients showed levels below 50 mg. of sugar. One value was so low as to be unreadable, 1 stood at 17 mg., 3 between 20 and 25 mg. and 28 between 30 and 39 mg. Yet none of the patients showed signs of seizure when the values were at these levels. The quantitative readings of the bromide content of the blood were sufficiently low to enable one to say that convulsions were not prevented as the result of medication. Many of the patients were not receiving any medication. In 7 instances attacks appeared from two to twelve hours after the hypoglycemic state developed. All these patients had been having attacks independent of the injections of insulin.

It appears, therefore, that acutely induced hypoglycemic states do not precipitate epileptic seizures.

Harris, extending his idea that hyperinsulinism is the cause of some cases of epilepsy, suggested that bromides inhibit the secretion of insulin. We have therefore correlated the amount of bromide in the blood of our patients with the amount of sugar in the blood during fasting and the character of the dextrose tolerance curve.

36. Harris, Seale: Epilepsy and Narcolepsy Associated with Hyperinsulinism, J. A. M. A. **100**:321 (Feb. 4) 1933.

37. Griffith, J. P. C.: Hypoglycemia and the Convulsions of Early Life, J. A. M. A. **93**:1526 (Nov. 16) 1929.

In 28 cases a determination of the bromide content of the blood was made at the same time as the sugar study. Despite the fact that many of the patients showed a high level of bromide in the blood (up to 300 mg. per hundred cubic centimeters), the fasting level for sugar for the group or for an individual patient showed no departure from that of the rest of the patients.

CONCLUSIONS

The fasting levels for dextrose of a series of 90 patients suffering from epilepsy were within normal limits. There was no relation between this level and the age, weight or sex.

There was no relation between the fasting levels for sugar and the precedence of succession of attacks; nor could the levels be correlated with the type of epilepsy, organic or idiopathic.

Oral dextrose tolerance tests were performed with blood from the finger for 90 of these patients. The readings fell essentially in the normal zone. Twenty-six per cent were high, 21 per cent low and 53 per cent normal. The same lack of correlation noted in the sugar studies during fasting was observed here. There was no evidence of an increased or decreased tolerance.

Further work on large groups of normal subjects is indicated to determine the significance of the various curves obtained in the dextrose tolerance tests. It is possible that when such studies are made, the variability of our curves may assume some importance in relation to a possible defective homeostasis of the body to dextrose stimulation.

Glycosuria occurred during the dextrose tolerance test in 20 per cent of the cases. There was none at fasting levels. The renal threshold for our patients averaged 188 mg. of blood sugar. This is slightly above that given for normal subjects. There was no evidence of a decreased tolerance.

Insulin tolerance tests performed by the subcutaneous method on 70 patients revealed a tendency for the lowest level to be attained at the end of the first hour and a distinct failure for the curve to return at the end of the third hour. No correlations with the age, weight, type of epilepsy, etc., could be found in the response of the patients to insulin.

The insulin tolerance test seems to indicate a failure of homeostasis because of the relatively many instances in which there was a failure to return at all after three hours. These curves should be compared with others subsequently obtained in large series of normal subjects.

A hypoglycemic state produced in 70 patients failed to precipitate an epileptic seizure.

Concentration of bromide in the blood at high or low levels failed to produce any alteration in the level of the blood sugar.

RETENTION AND UTILIZATION OF SMALL AMOUNTS OF ORALLY ADMINISTERED IRON

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It has been demonstrated repeatedly that a satisfactory hemoglobin response in cases of hypochromic anemia ensues with the administration of large amounts of iron,[1] but it is recognized that the amount of iron so administered is greatly in excess of that utilized in hemoglobin regeneration. We[2] have shown that from 14 to 71 per cent of the administered iron is retained by the body when 3 Gm. of iron and ammonium citrates (yielding approximately 500 mg. of metallic iron) is given daily by mouth. Only a small portion of this (1.2 to 3.4 per cent) is utilized in the building of hemoglobin.

The hemoglobin response to small amounts of iron has been found to be less satisfactory, although the amount of iron would seem to be adequate for hemoglobin regeneration if it were properly absorbed from the gastro-intestinal tract. The present study was undertaken to determine the amount of iron retained when these more moderate doses of iron and ammonium citrates were administered. Balance studies were conducted, as described in a previous communication.[2] For a three day period of adjustment before observations were begun, the patients were given the diet which they were to receive throughout the period of study. This was followed by a control period, during which no medicinal iron was administered and the intake of iron was obtained from the food alone. This period and all subsequent ones were of six days' duration.

Supported in part by a grant from Eli Lilly & Co.

From the Department of Internal Medicine, the State University of Iowa.

This work was begun in association with Dr. C. W. Baldridge, who died on Nov. 22, 1934.

1. Bethell, F. H.; Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Diagnosis and Treatment of the Iron-Deficiency Anemias, J. A. M. A. **103**:797 (Sept. 15) 1934. Meulengracht, E.: Large Doses of Iron in the Different Kinds of Anemia in a Medical Department, Acta med. Scandinav. **58**:594, 1923. Goodall, A.: Treatment of Anemia: Chlorosis and Secondary Anemia, Lancet **1**:1216, 1926.

2. Fowler, W. M., and Barer, A. P.: Retention and Utilization of Orally Administered Iron, Arch. Int. Med. **59**:561 (April) 1937.

The essential clinical features and the hematologic data for each patient are given in tables 1 and 2. A minimal tuberculous lesion was found in the apex of the left lung of patient 1 on roentgenologic examination, but it seemed unlikely that anemia of this degree would be produced by otherwise asymptomatic tuberculosis. No history of excessive loss of blood was obtained. In patient 6 the anemia was apparently idiopathic in origin, while in the other four patients it was undoubtedly due to a chronic loss of blood.

TABLE 1.—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	40	F	Hypochromic anemia	Minimal pulmonary tuberculosis in apex of left lung
2	23	F	Hypochromic anemia; hemorrhage	Profuse menstrual bleeding for several years; submucous fibroid tumor removed
3	33	F	Hypochromic anemia; hemorrhage	Gross hematuria with "fish worm" clots for two years after blow on abdomen; no history of other loss of blood; pyelograms revealed crossed ectopic fused kidney; no other cause for anemia found; hematuria ceased spontaneously
4	21	F	Hypochromic anemia; hemorrhage	Profuse uterine bleeding; cervical polyp removed; hyperplastic endometritis
5	44	F	Hypochromic anemia; hemorrhage	Profuse menstrual bleeding; hysterectomy performed for fibromyoma
6	46	F	Hypochromic anemia; idiopathic	Migraine; splenomegaly; visceroptosis; normal renal function; normal basal metabolic rate; achlorhydria

TABLE 2.—*Hematologic Data*

Patient	Hemoglobin, Percentage	Hematocrit Reading, Percentage	Erythrocytes, Percentage	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	50	77	83	0.60	0.92	0.64	0	—16
2	46	73	68	0.67	1.07	0.63	Normal	— 9
3	25	40	56	0.44	0.71	0.62	Normal	+ 5
4	55	70	62	0.88	1.12	0.78	Normal	+ 1
5	52	61	82	0.63	0.74	0.85	0	—18
6	54	63	87	0.62	0.72	0.85	0	— 2

The results of the iron balance studies, together with the nitrogen and phosphorus balances, are given in table 3, and a summary of the iron studies is given in table 4. The first five patients received from 170 to 180 mg. of iron per day, which represented the administration of approximately 5 grains (0.3 Gm.) of iron and ammonium citrates three times daily, given as an aqueous solution of the brown scales. Patient 6 received 7½ grains (0.48 Gm.) of the drug three times daily, with an average daily intake of iron of 243.5 mg.

All the patients were in negative iron balance during the control period, but with the administration of iron and ammonium citrates iron was retained in every instance. The amount retained, as might be expected, was much less than that retained by those patients previously

reported on [2] who had received larger amounts of the drug. The daily retention of iron varied from 26.2 to 114.4 mg. All the patients were in positive iron balance continuously, but the retention in the first period was somewhat greater than during the second six day period. Patient 4 retained 1,479.9 mg. of iron in eighteen days, and patient 5 retained 1,074.6 mg. in twenty-four days. The percentage of the administered iron which was retained by the body varied from 10.3 to 45.1, with

TABLE 3.—*Nitrogen, Phosphorus and Iron Balances*

		Nitrogen, Mg.			Phosphorus, Mg.			Iron, Mg.			Red Blood Cells, Millions	Hemoglobin, Gm. per 100 Cc.
Patient	Period	Intake	Excretion	Balance	Intake	Excretion	Balance	Intake	Excretion	Balance		
1	1	9.78	11.12	−1.34	1.44	1.18	+0.26	11.9	18.5	− 6.6	4.12	7.188
	2	9.85	10.72	−0.87	1.43	1.16	+0.27	180.5	125.3	+ 55.2	4.13	7.393
2	1	10.77	10.82	−0.05	1.53	1.28	+0.25	13.0	25.7	− 12.7	3.50	6.273
	2	11.85	9.81	+2.04	1.62	1.37	+0.25	182.7	139.5	+ 43.2	3.77	6.345
3	1	10.73	11.54	−0.81	1.55	1.32	+0.23	13.0	25.9	− 12.9	2.73	4.150
	2	11.64	7.00	+4.64	1.60	1.76	+0.16	182.6	139.4	+ 43.2	3.03	4.680
	3	13.34	7.01	+6.33	1.85	2.01	−0.16	183.9	141.8	+ 42.1	3.58	5.355
4	1	10.37	5.60	+4.77	1.50	1.33	+0.17	12.7	22.2	− 9.5	3.19	7.800
	2	11.04	5.26	+5.78	1.55	1.59	−0.04	182.0	111.0	+ 71.0	3.56	7.800
	3	11.04	5.86	+5.18	1.55	1.37	+0.18	182.0	120.8	+ 61.2	3.99	9.020
	4	11.04	6.07	+4.97	1.55	1.45	+0.10	182.0	67.6	+114.4	4.08	10.520
5	1	9.96	10.20	−0.24	1.42	1.38	+0.04	10.2	14.5	− 4.3	4.22	7.365
	2	9.97	9.55	+0.42	1.42	1.13	+0.29	170.6	117.3	+ 53.3	4.40	8.005
	3 *	9.95	10.11	−0.16	1.43	1.57	−0.14	170.7	156.4	+ 14.3	4.25	8.340
	4 †	9.97	11.76	−1.79	1.42	1.43	−0.01	170.6	105.2	+ 65.4	4.68	10.370
	5	9.97	11.72	−1.75	1.42	1.19	+0.23	170.6	122.0	+ 48.6	4.93	11.360
6	1	9.94	0.48	+0.46	1.18	0.92	+0.26	10.0	10.7	− 0.7	5.02	7.710
	2	10.08	9.43	+0.65	1.18	0.86	+0.32	253.5	227.3	+ 26.2	4.71	7.440

* Five day period.
† Thirty-six days between periods 3 and 4. Medication was continued.

TABLE 4.—*Average Daily Iron Balances by Periods*

	Iron Balance, Mg.						
Patient	Control Period	Period 1	Period 2	Period 3	Period 4	Total Iron Retained, Mg.	Average Daily Retention of Iron, Mg.
1	− 6.6	+55.2	.....	.....	.....	330.7	55.2
2	−12.7	+43.2	.....	.....	.....	259.3	43.2
3	−12.9	+43.2	+42.1	.....	.....	511.8	42.6
4	− 9.5	+71.0	+61.2	+114.4	.....	1,479.9	82.8
5	− 4.3	+53.3	+14.3	+ 65.4	+48.6	1,074.6	44.7
6	− 0.7	+26.2	.....	.....	.....	156.8	26.2

an average retention for the six patients of 26.6 per cent. This is slightly lower than the average of 32.6 per cent reported for the group of patients receiving 500 mg. of iron per day,[2] but the difference is not great enough to be of significance.

The severity of the anemia did not play a part in determining the amount of iron retained. The two patients showing the highest and the lowest percentage of retained iron had almost identical readings for hemoglobin; and the patient with the lowest value for hemoglobin retained slightly less iron than the average for the entire group.

It is recognized that adequate control periods and absence of recent loss of blood are necessary in attempting to evaluate the effectiveness of iron in hemoglobin regeneration, and these factors were given due attention in selecting the patients for this study. The usual reticulocyte response was obtained after the administration of iron, and the rate of hemoglobin regeneration was satisfactory. Patients 1, 2 and 6 are not considered in this connection, since they received iron for only one six day period, a period too short to be of significance in considering hemoglobin regeneration with orally administered iron. For the remaining three patients the daily increase in hemoglobin was 0.1, 0.151 and 0.082 Gm. per hundred cubic centimeters of blood, respectively. This falls short of the optimum hemoglobin response given by Heath [3] but nevertheless is satisfactory in view of the small amount of iron administered to these patients.

TABLE 5.—*Retention and Utilization of Iron*

Patient	Total Intake of Iron, Gm.	Total Iron Retained, Gm.	Original Hemoglobin Content, Gm. per 100 Cc.	Total Increase in Hemoglobin, Gm.	Average Daily Gain in Hemoglobin, Gm. per 100 Cc.	Iron, Percentage Retained	Iron, Percentage Used as Hemoglobin	Retained Iron, Percentage Used as Hemoglobin
1	1.082	0.330	7.18	.....	.....	30.5	....	....
2	1.096	0.259	6.27	.....	.....	23.6	....	....
3	2.198	0.511	4.15	60.25	0.100	23.2	8.2	35.3
4	3.276	1.479	7.80	136.00	0.151	45.1	12.4	27.5
5	3.923	1.074	7.36	98.25	0.082	27.1	7.5	27.4
6	1.520	0.156	7.71	.....	.....	10.3	....	....

If it is assumed, as it was by Heath,[3] that the volume of blood in each case was 5 liters and if the approximate total gain in hemoglobin is calculated for each, it is found that from 7.5 to 12.4 per cent of the orally administered iron was used in the formation of hemoglobin (table 5). The average for the three patients was 9.3 per cent, which is considerably larger than the 1.9 per cent utilized when large amounts of iron were administered [2] and is greater also than the 3.4 per cent reported by Heath. Of the iron which was retained by the body, it was found that 30 per cent was used in the formation of hemoglobin. The remaining 70 per cent was presumably stored in the spleen, liver and other parts of the reticulo-endothelial system.

COMMENT

One is not justified in assuming, on the basis of the three patients studied in respect to hemoglobin regeneration, that these small amounts of iron are sufficient to produce a satisfactory hemoglobin response in

3. Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. **51**:459 (March) 1933.

all patients. It does show, however, that in certain uncomplicated cases this amount of iron will suffice both for a satisfactory increase in hemoglobin content and for a replenishment of the depleted stores of iron. In all the cases a sufficient amount of iron was retained to supply the needs of the body in this respect. The amount of iron retained was much less than that with the administration of 3 Gm. of iron and ammonium citrates per day, but the average daily positive balance of from 14.3 to 114.4 mg. was sufficient for the body requirements, even with the abnormal demands resulting from prolonged anemia. The percentage of the iron utilized in the formation of hemoglobin was somewhat greater than with the larger intake of iron, although such comparisons may be misleading, since many factors other than the retention of iron may influence hemoglobin regeneration. The percentage of the retained iron which was utilized in the formation of hemoglobin is interesting, as it shows that a large part of the iron is deposited in the body in some form other than hemoglobin. A considerable portion is presumably used to replenish the depleted stores of iron, since animal experimentation has shown that the iron content of the reticulo-endothelial system is increased after the administration of iron.[4] Although abundant iron is available for its formation, hemoglobin regenerates more slowly than with the administration of larger amounts of iron. The reason for this is not apparent. Whipple [5] has asserted that the excess iron from larger doses exerts a "salt effect." It has been assumed also that iron may act as a direct stimulant of bone marrow, although definite proof of this is lacking.

If the administration of large amounts of iron over a long period has caused some concern as to its possible deleterious effect on the body, it is of interest to note that an adequate amount can be retained from smaller doses. Massive doses seem to be advisable early in the course of therapy, because of the more rapid hemoglobin response; but for a maintenance dose smaller amounts suffice, and they lessen the potential danger from prolonged massive doses.

SUMMARY

The administration by mouth of iron and ammonium citrates in doses of 1 and 1.5 Gm. daily leads to the retention of iron in such amounts as will replenish the depleted stores of iron and produce a fairly rapid increase in the hemoglobin content.

4. Polson, C. J.: The Storage of Iron Following Its Oral and Subcutaneous Administration, Quart. J. Med. **23**:77, 1929. Robscheit-Robbins, F. S.: The Regeneration of Hemoglobin and Erythrocytes, Physiol. Rev. **9**:666, 1929.

5. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood Regeneration in Severe Anemia: Optimum Iron Therapy and Salt Effect, Am. J. Physiol. **92**: 362, 1930.

COCCIDIOIDES INFECTION

PART I

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Because the first known case in North America of what is now called coccidioidal granuloma was reported from Cooper Medical College, in San Francisco, by Rixford and because the disease was proved by Ophüls, also of Cooper Medical College, to be caused by infection with a pathogenic fungus and not with a protozoan organism, coccidioidal granuloma has always aroused much interest in that school, which later became the Stanford University School of Medicine. Many patients with coccidioidal granuloma, representing practically all the known clinical types of the disease, have been studied and treated in the hospitals of this institution. For many years there has been more or less intensive study of the fungus in the laboratories of the medical school.

The generally accepted conceptions of the disease have gradually changed during the past thirty years, from the time when the disease was believed to be very rare and almost always fatal until the present, when about thirty new cases are reported to the State Department of Health in California each year, with a reported mortality rate during the past eight years of only 49.7 per cent. In all, four hundred and fifty cases have been reported in California.

The reports that will follow are based on a study of infection with Coccidioides in human beings and domestic animals in California, supplemented by intensive experimental work which has been conducted during the past few years.

The number of articles on coccidioidal granuloma published in the medical literature of the United States is relatively great in proportion to the number of known cases in this country. The first case reported was from Buenos Aires in 1892.[1] The first report of a case in North America (California) was made in 1894.[2] A number of cases

From the Department of Public Health and Preventive Medicine, Stanford University School of Medicine.

1. Wernicke, R.: Ueber einen Protozoenbefund bei Mycosis fungoides (?), Centralbl. f. Bakt. **12**:859, 1892.

2. (*a*) Rixford, Emmet: A Case of Protozoic Dermatitis, Occident. M. Times **8**:704, 1894. (*b*) Rixford, Emmet, and Gilchrist, T. C.: Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs, Johns Hopkins Hosp. Rep. **1**:209, 1896.

have been reported from Colombia and Brazil of a similar infection with fungus which has been described as Paracoccidioides by de Almeida,[3] who named the organism Coccidioides brasiliensis. Several reports have appeared in the British and European medical literature, but they have dealt almost exclusively with cases which had occurred in North or South America.

The great majority of the articles published in this country have been case reports and have suggested methods of therapy, usually unsuccessful. A few authors in the United States, notably Ophüls,[4] Ricketts,[5] Wohlbach,[6] MacNeal and Taylor[7] and Ahlfeldt,[8] have made careful studies of the fungus Coccidioides and have attempted to correlate the peculiar endosporulating spherules which are found within the tissues with the fine septate mycelial growth which develops on the culture medium.

The mortality rate in cases reported in the United States has been high, but this has undoubtedly been due to the fact that, for the most part, only cases of advanced stages of the disease have been recognized, and until recently only the cases of severe and fatal involvement have been described in the literature. It is a fact that when the infecting agent has become disseminated in the body, a severe generalized infection, with multiple lesions in various parts of the body, develops and usually progresses rapidly until the death of the patient. In 1905 Ophüls[9] reported on twelve patients, of whom ten were dead and one had been lost sight of at the time of the report. When I[10] reported on a col-

3. de Almeida, F. P.: Estudose comparativos do granuloma coccidioidica nos Unidos e Brasil: Novo genero para o parasito brasiliero, Ann. Fac. de med. de São Paulo **5**:125, 1930; abstr., Compt. rend. Soc. de biol. **105**:315, 1930.

4. (*a*) Ophüls, William, and Moffitt, H. C.: A New Pathogenic Mould (Formerly Described as a Protozian, Coccidioides Immitis; Pyogenes), Philadelphia M. J. **5**:1471, 1900. (*b*) Ophüls, William: Further Observations on a Pathogenic Mould Formerly Described as a Protozoan (Coccidioides Immitis, Coccidioides Pyogenes), J. Exper. Med. **6**:443, 1905.

5. Ricketts, H. T.: Oidiomycosis (Blastomycosis) of the Skin and Its Fungi, J. M. Research **1**:373, 1901.

6. Wohlbach, S. B.: The Life Cycle of the Organism of "Dermatitis Coccidioides," J. M. Research **13**:53, 1904.

7. MacNeal, W. J., and Taylor, R. M.: Coccidioides Immitis and Coccidioidal Granuloma, J. M. Research **30**:261, 1914.

8. Ahlfeldt, Florence E.: (*a*) Studies in Coccidioidal Granuloma, Arch. Path. **2**:206 (Aug.) 1926; (*b*) Special Observations on the Morphology of Coccidioides Immitis, J. Infect. Dis. **44**:277, 1929.

9. Ophüls, William: Coccidioidal Granuloma, J. A. M. A. **45**:1291 (Oct. 28) 1905.

10. Dickson, E. C.: Oidiomycosis in California, with Especial Reference to Coccidioidal Granuloma, Arch. Int. Med. **16**:1028 (Dec.) 1915.

lection of forty cases in 1915, I made the statement that "the prognosis is extremely grave. The outcome of the disease is almost always fatal." The same opinion has been expressed by many authors. In my report in 1915, however, were recorded two cases in which early amputation or resection of local lesions in the extremities was followed by clinical recovery and one case in which a healed or arrested lesion was discovered at autopsy in the lung of a man who had died of carcinoma of the stomach. Similar healed or arrested lesions in the lungs have since been observed at autopsy in a number of patients in Stanford University and other hospitals, so that there can be no doubt that the lesions of coccidioidal granuloma have a tendency to heal. Moreover, one occasionally encounters patients with more or less localized lesions, more often in the skin, in whom the course of the disease is stationary, sometimes for years, although such lesions rarely heal spontaneously.

More recently, observations have been made which indicate that there is much to learn about the initial manifestations of infection with Coccidioides. In 1929 I was afforded an excellent opportunity of studying, with Dr. P. H. Pierson, of the Stanford University Hospital, two patients with primary pulmonary infection. One of the patients had acquired the infection in our laboratory, and the other, an engineer, had acquired it in the oil fields of the San Joaquin Valley, where he had been exposed to a great deal of dust when engaged in construction work. Both patients had bronchopneumonia of moderate severity, and roentgenographic examination showed that the involvement was more intense in the bases of the lungs (fig. 1). In one instance the first diagnosis made by the roentgenologist was tuberculosis. The diagnosis of infection with Coccidioides was established in both cases by demonstration of the typical spherules of Coccidioides in the sputum, confirmed by culture and guinea-pig inoculation. After severe illness and protracted convalescence, both patients recovered, apparently completely, and have shown no subsequent indication of the infection. We have knowledge of two other patients who had a similar history, one of whom, described by Boyers,[11] has remained well for at least fifteen years. The later history of the other patient is unknown to us.

Another fact that has become evident is that in a number of instances in which the first manifestation of illness has been an acute "cold" or bronchopneumonia, this has been followed shortly by an outbreak of erythema nodosum, usually on the shins. I recently saw three patients with such acute involvement: the young man who acquired the infection in our laboratory, a student who spent his vacation working in an area where the disease is endemic and a woman who was

11. Boyers, L. M.: Therapy in Two Cases of Infection with Coccidioides Fungus, M. Herald **52**:61, 1933.

visiting in an area where the disease is endemic. The diagnosis was made in the first case as previously described, in the second by microscopic examination of biopsy tissue from a lesion on the neck and in the third by means of a cutaneous test with coccidioidin about two months after subsidence of the acute illness. The roentgenograms in the third case, like those in the case of laboratory infection previously mentioned, showed pulmonary involvement which at first was believed to be tuberculous, but after later examinations the roentgenologist concluded that the involvement could not be tuberculous because the lesions were clearing rapidly.

Dr. Mernie Gifford, of Bakersfield, Calif., has shown me records of three of fifteen patients with coccidioidal granuloma, admitted consecutively to the Kern County Hospital, in whom the first sign of illness was a "bad cold" with a cough or bronchopneumonia, associated with erythema nodosum. In all these patients there had been progression

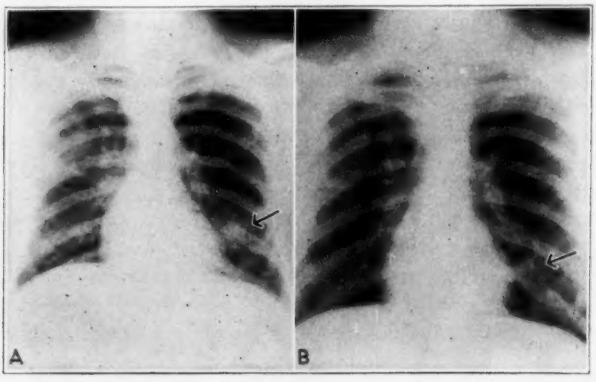

Fig. 1.—Roentgenograms of the chest in case 1. *A*, at the onset of illness on Sept. 18, 1929. Note the increased density toward the base of the left lung. *B*, one month later. Note that the basal infiltration is much less dense.

to the later stages of coccidioidal granuloma with disseminated lesions; but, according to Dr. Joe Smith, Health Officer of Kern County, erythema nodosum, often accompanied with a severe cold, is unusually common in San Joaquin Valley; there is a characteristic seasonal incidence and many of the patients recover promptly. The first of our patients with erythema nodosum is well after more than six years; one of the two patients recently seen shows no signs of the acute illness other than the clearing lesions in the lungs, but the third still shows involvement of the cervical lymph nodes.

It is obvious, therefore, that more information concerning the earliest manifestations of coccidioidal granuloma in human beings and

of the method of spread of the fungus in the tissues is urgently needed. Evidence is accumulating that death from coccidioidal granuloma occurs only when there is the extensive involvement of the tissues which follows dissemination of the organism in the blood stream and that heretofore only this late disseminated type has been generally recognized. In my opinion, one would be equally justified in drawing all conclusions of tuberculosis from a study of cases of acute miliary involvement in which the tubercle bacilli have been widely disseminated by the blood stream as in basing all knowledge of coccidioidal granuloma on terminal stages in which the organisms have become widely disseminated. Since it is known that lesions of coccidioidal granuloma may be very sluggish, that there is a definite tendency for the lesions to heal and that at least some of the victims of the infection recover or at least remain free from symptoms for several years, it is essential that attempts be made to learn more of the initial manifestations of infection with this organism and that judgment be reserved as to the true incidence of the disease until more information along these lines is at hand.

The fact that almost all the patients in whom early infection with Coccidioides has been recognized had initial "colds" or bronchopneumonia tends to substantiate the stated belief of Ophüls and others that the disease is usually acquired by inhaling the spores of the fungus. That inhalation of the spores may cause the onset of acute infection was shown, almost with experimental precision, in the case of the young man who acquired the disease in our laboratory. The exact time of the exposure was known; it occurred on the first day he was permitted to work with the fungus. By an unfortunate mistake he removed the cover from a Petri dish containing an old, partially dried culture of Coccidioides and observed a fine brownish cloud rise from the culture. Ten days later he had a "cold" which progressed to bronchopneumonia. This hypothesis has been supported by the fact that Beck, Traum and Harrington [12] found that in infected cattle the bronchial and mediastinal glands, and usually only these, are involved. Moreover, necropsy in human beings often shows that the peribronchial lymph glands reveal an old chronic type of lesion which contrasts sharply with the more recent types of lesions observed elsewhere. These older lesions obviously antedate the more recent lesions which are distributed generally throughout the body. It is not difficult to believe that they are produced by lymph draining from acutely infected lungs in which the lesions subsequently clear and that they constitute the foci in which the infective agent persists in the body and is eventually disseminated by involvement of a blood vessel.

12. Beck, D.; Traum, J., and Harrington, E. S.: Coccidioidal Granuloma: Occurrence in Animals, J. Am. Vet. M. A. **78**:490, 1931.

Of course cases have been reported in which it seemed certain that cutaneous lesions were primary, owing to local inoculation with the spores of the fungus. The first case described by Rixford [2a] was that of a laborer who had a verrucous lesion on the back of the neck, where his collar band rubbed, that persisted for eight years before it began to spread to any great degree. In case 33 which I described in 1915,[10] the first lesion was at the site of an abrasion on the hand which was caused by picking walnuts. Seilin [13] reported the case of a cigar maker who had a lesion on the hand and who apparently showed no signs of systemic involvement. Guy and Jacob [14] described a case in which, after a prick on the thumb with a cactus spine, the first small abscess developed at the site of the puncture and was followed by a number of similar lesions along the track of the lymphatics until the axilla was reached. It was only later that the patient presented evidence of general dissemination of the parasite. However, the appearance of the first visible lesion on the skin does not necessarily mean primary involvement of the skin. In the case of the student in our series of patients showing acute involvement, the first demonstrable lesion after the acute onset was a small "pimple-like" pustule in the skin of the neck from which spherules of Coccidioides were isolated.

In commencing our study of the manner of spread in infection with Coccidioides it seemed desirable to review the reported observations on the characteristics of the fungus on culture medium and in infected subjects. This part of the work was carried through by Dr. H. D. Chope, of Newton, Mass., when he was a member of this department. His method of procedure differed from the methods that had previously been reported in that he made a more detailed study of individual spherules which were isolated from pus and injected the fungus into the testicles of guinea-pigs in order to observe the various changes which occur in animal tissues.

When Posadas discussed Wernicke's case [15] and Rixford and Gilchrist [2] reported their cases, they described carefully the peculiar spherules and method of endosporulation. They stated the opinion that they were dealing with a protozoon of the Coccidia type; hence the name Coccidioides. Ophüls and Moffitt [4a] discovered that the infecting organism is not of the animal kingdom but a fungus with a characteristic production of endosporulating spherules within the tissues, although it grows on culture medium as a mass of fine septate mycelium.

13. Seilin, J.: Report of a Case of Dermatitis Coccidiosa, M. Rec. **95**:360, 1919.

14. Guy, W. H., and Jacob, F. M.: Granuloma Coccidioides, Arch. Dermat. & Syph. **16**:308 (Sept.) 1927.

15. Posadas, Alexandre: Psorospermiose infectante généralisée, Rev. de chir. **21**:277, 1900.

The mature spherules in the tissues average about 30 microns in diameter, although young forms may be much smaller and some endosporulating forms may be considerably larger. The outer wall is a thick, hyaline, double-contoured capsule which in some instances may be covered with spines or, better, prickles. Reproduction within the tissues is always by endosporulation, never by budding, the endospores being liberated by rupture of the capsule, which remains as an empty "envelop." When pus is evacuated and planted on culture medium or when the pus is allowed to stand in a container, mycelia develop from the spherules and form the mold growth previously mentioned. However, development of hyphae never takes place within living animal tissue, and maturation of the spherule with endospores has never been observed except in living animals.

If one begins with the spherule which occurs in pus, what one may describe as the first, or vegetative, phase in the various stages of development is the development of hyphae to form the mold growth. Ophüls [4b] reported this in detail in 1905. He studied the development of individual spherules suspended in broth in hanging drop preparations. His description was as follows:

> The thick membrane which surrounds the latter [spherule] becomes very thin in one place and begins to evaginate over the bud from the enclosed protoplasm. These buds soon assume the form of coarse, more or less cylindrical threads which are either straight or somewhat wavy. At first the protoplasm forms one continuous mass in the main body [of the spherule] and buds, but after a while septa appear at various places in the buds, and sometimes partitions also form between the bud and the main body.

Wohlbach [6] stated that the mycelia sprout from the capsule, but MacNeal and Taylor [7] and Chope said they agreed with Ophüls that they begin as evaginations of the protoplasm through the capsule. Chope also observed instances in which the sprouting filaments could be seen originating from the endospores in pus before they had been released from the mother spherule (fig. 2*d*), but of course the pus had been evacuated, as no indication of hypha formation has ever been observed until after the spherules have been removed from the animal body. The formation of hyphae is as specifically limited to the growth of the organism on medium outside the body as reproduction by endosporulation is restricted to development within the tissues.

As was pointed out by Ophüls,[9] all spherules do not sprout hyphae, but there is nothing definite by which a spherule that will form hyphae can be distinguished from one that will not. Ophüls stated the belief that they must be mature. Ahlfeldt [8b] described minute bodies in the compartments of mycelium from which the spherules are formed, which suggested sexual elements and the possibility of a bisexual life, but she

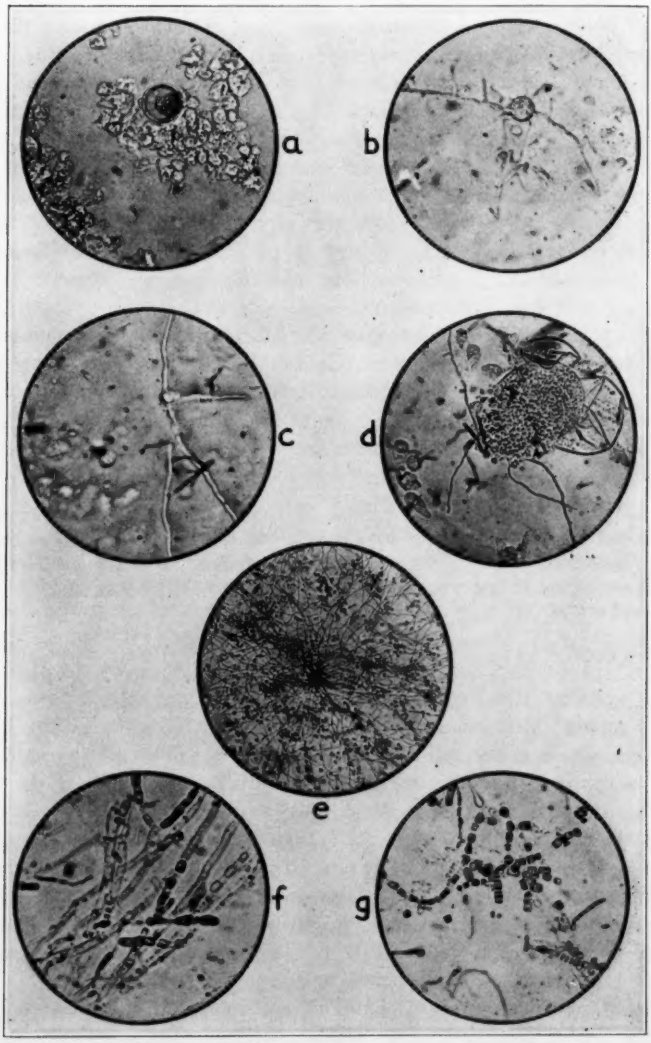

Fig. 2.—Section *a* shows a spherule of Coccidioides in pus; *b*, mycelia growing from the spherule; *c*, mycelia growing from a free endospore; *d*, mycelia growing from endospores which have recently burst the capsule but have not been dispersed; *e*, a portion of the growth; *f*, mycelia, with the formation of septums and the beginning of chlamydospore formation, and *g*, well formed chlamydospores, some of them broken free from the mycelium.

did not observe conjugation. I have not seen anything that would support such a theory either in mycelial segments or in the spherules.

When the spherule has sprouted and produced branching mycelia, growth occurs on culture medium as a mold, presumably identically as it develops in nature. The organism will maintain its type and virulence for years when transplanted to new medium from time to time. Passage through an animal with a cycle of spherule formation does not appear to be necessary for the survival of the organism. Certain cultures have been maintained in our laboratory for at least ten years by simply transferring the organisms to new medium from time to time, and they do not seem to have lost any of their infectivity or virulence for laboratory animals in that time.

In broth the fungus grows near the bottom of the test tube as white fluffy balls consisting of an intricate meshwork of fine branching mycelium. On an agar plate it may develop into a discrete round fluffy colony, 2 inches (6 cm.) or more in diameter. On agar slants it occurs first as small white nodules made up of branching hyphae which soon coalesce until the whole surface of the medium is covered with the fluffy white growth, which has numerous fine mycelia penetrating the medium and firmly anchoring it. As the culture ages the growth becomes more brownish, gradually the fluffy appearance is lost and the culture appears as a somewhat membranous cover over the medium, which is finely granular—as if dusted with fine flour. These old cultures are particularly dangerous to handle, as the fine deposit consists of light chlamydospores that are readily disseminated through the air. It was such a dissemination which was observed when the cover was removed from a Petri dish culture by the young man who became infected in our laboratory.

The optimum temperature for the sprouting of the spherules appears to be about 30 C., but thereafter the growth of the fungus appears to be somewhat more luxuriant at 37 C. No sprouting or growth was observed at 42.5 C. Pus which contains spherules may be left in the icebox for two months without any sprouting of the spherules, but if the spherules are then placed at 30 or 37.5 C. they sprout promptly and there does not seem to be anything remarkable about the growth which results.

The fungus grows readily on practically all the ordinary culture mediums and usually is not overgrown by bacteria, although the bacterial growth may be active for almost two days before the colonies of fungus appear. Growth occurs also, although less actively, on synthetic inorganic mediums.

Coccidioides has never been observed in nature. On one occasion Stewart and Meyer [16] succeeded in isolating it from soil secured in an

16. Stewart, R. A., and Meyer, K. F.: Isolation of Coccidioides Immitis (Stiles) from the Soil, Proc. Soc. Exper. Biol. & Med. **29**:937, 1932.

area where the disease is endemic, but its habitat in nature is unknown. It is suspected that the infectivity for human beings and animals depends on its growth in regions where in winter there is rain, with relatively little cold, and where the summers are dry, permitting the distribution of chlamydospores with dry soil which is stirred up as dust.

The formation of chlamydospores is as follows, as described by Ophüls:[1b] first the division of the aerial hyphae into segments by firm partitions, then the development of thickened capsules and finally the separation by fragmentation of the now brittle hyphae. When the chlamydospores are liberated, they occur singly or in groups which may remain attached to each other by the persisting portions of the hyphae which connect them. If these chlamydospores are transferred to fresh medium, mycelia promptly sprout, and new colonies are formed. The first phase of the development is shown in figure 2.

The second, or parasitic, phase of development, that of the formation of spherules in the tissues, has been described by Ophüls,[1b] Wohlbach[6] and MacNeal and Taylor.[7] Chope approached the problem by injecting the organisms into the testicles of guinea-pigs and killing one animal every four hours. There has been some difference of opinion as to whether the spherules develop from chlamydospores only or whether they may develop also from hyphae that do not contain chlamydospores. Ophüls stated that unless spores are present the fungus is noninfective, but Wohlbach stated that the undifferentiated hyphae are spherulogenic. In order to check this, Chope prepared cultures from infectious pus and from a stock culture and injected them into the testicles of guinea-pigs after two, four and seven days of incubation. The two day cultures contained no evidence of chlamydospores, the four day cultures contained mycelia with early stages of differentiation and the seven day cultures contained moderate numbers of well formed chlamydospores. The results of his test are shown in the accompanying table.

Results of Inoculations with Different Cultures *

Day After Inoculation on Which Animal Was Killed	Age of Culture					
	2 Days		4 Days		7 Days	
	P	S	P	S	P	S
3d	—	—	—	+	—	+
5th	—	+	+	+	+	+
7th	+	+	+	+	+	+
9th	+	+	+	+	+	+

* P indicates mycelia cultured from pus; S, mycelia cultured from a stock culture; —, absence of spherules or pus in test animal, and +, presence of spherules in pus from test animal

The experiment showed that spherules will form from mycelia which do not contain demonstrable chlamydospores but that it takes longer for them to appear than when mycelium in which chlamydospores are

present is used. Moreover, it indicated also that a two day culture from a stock culture produces spherules more quickly than a two day culture from infectious pus. Whether the undifferentiated mycelia go through the stage of chlamydospore formation after they are injected was not demonstrated.

The sequel of events which occur after the fungus is injected into the testicle is the same as that described by Ophüls [1b] and by Wohlbach,[6] differing only in detail. Because experiments had shown that the formation of spherules is more prompt when the mycelia contains mature chlamydospores, the inoculum in our experiments was standardized to the extent that only eight and ten day cultures of mycelium were used, because by this time chlamydospores are well developed. Each culture was examined at intervals microscopically to ascertain the stage of chlamydospore formation before it was injected. The fact that our experiments showed a shorter interval for the completion of the intratissue cycle than others that have been reported is undoubtedly due to this feature.

Figure 3 shows the stages through which the chlamydospores pass before they form true spherules and mature by forming endospores. It will be noted that after the injection of the suspension of chlamydospores the outline of the hyphae may be intact on the third day but that the chlamydospores are somewhat rounded and their outer capsule is well defined. At forty-four hours some of these chlamydospores are well rounded out although still connected together as in the hyphae. At sixty hours the spherules are well developed and are as large (about 30 mm.) as the immature spherules are likely to be when observed in pus from a patient. By seventy-two hours some of the spherules are filled with endospores, and in ninety-six hours some of them have burst, showing the manner in which the endospores are liberated and how the "envelop" is formed.

On rare occasions we have observed in culture, under anaerobic conditions, spherical enlargements of the chlamydospore segments of the hyphae (fig. 3*f*). In their size and the character of their membrane they resemble the partly matured spherules which may be seen free in pus, but they are not separated from the mycelial growth, and we have never observed any indication of the formation of endospores within them. On only one occasion did we observe a similar type of development in the hyphae of a spherule which had sprouted in pus that had been left standing in an open vessel at room temperature (fig. 3*g*). MacNeal and Taylor [7] observed one such spherule formation in an anaerobic culture but did not find any in aerobic cultures. During a somewhat limited study of anaerobic cultures we were not able to prove

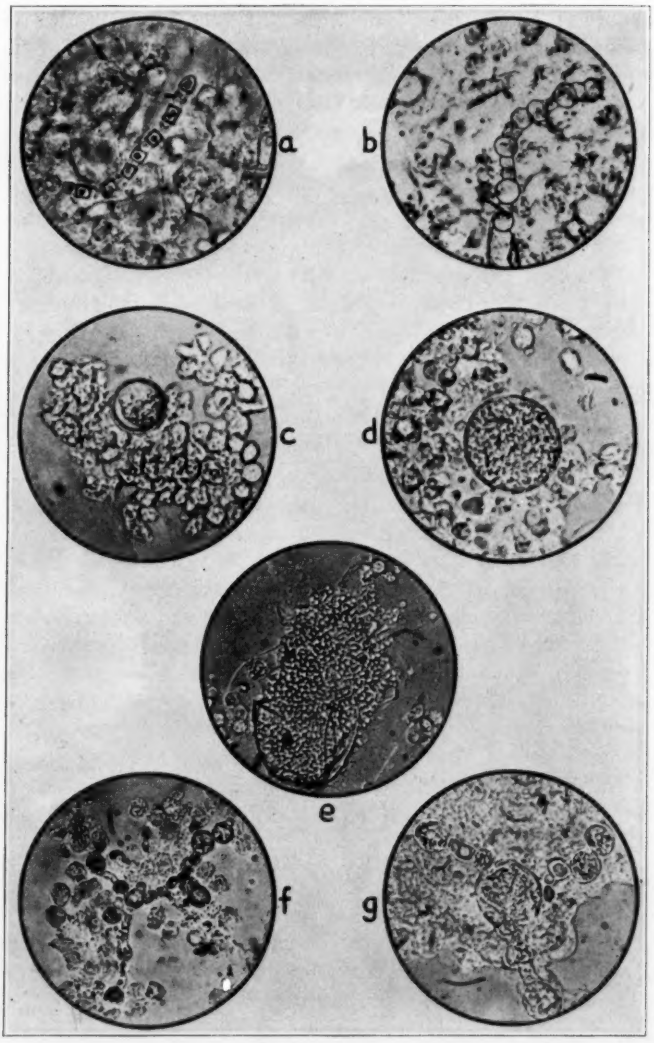

Fig. 3.—Section *a* shows mycelium in pus with beginning differentiation of the chlamydospores; *b*, mycelium (after forty-four hours) with the chlamydospores having become more circular (retouched); *c*, a single spherule in pus (sixty hours); *d*, a spherule in the stage of endosporulation (seventy-two hours after injection); *e*, ruptured spherule, indicating how the "envelop" is formed and how endospores are liberated (ninety-six hours after injection); *f*, mycelium with small spherical bodies in anaerobic culture, and *g*, mycelium with small spherical bodies in "old" pus which had stood at room temperature.

that the formation of spherules depends wholly on the low oxygen tension, because usually no such spherule formation was seen in anaerobic cultures.

Occasionally endosporulating spherules with a different appearance are encountered in pus or infected tissues; i. e., the spherules have large central vacuoles and show peripheral arrangement of the endospores. Rixford [2b] first described these in the report of his second case and said that they might represent a different species of the organism. He suggested the name Coccidioides pyogenes and said he believed they represented a more virulent form than Coccidioides immitis. Mazzai has described a similar form which was considered to be a new species and to which Fonseca gave the name Pseudococcidioides Mazzai. The article describing this form was not available, but de Almeida [17] in discussing it, makes the following quotation:

> . . . the formation of the spores of Pseudococcidioides Mazzai is accomplished by the appearance of radiating openings in the protoplasm which divide the organism (spherule) into cones. Later, new divisions are formed but are parallel to the membrane of the cell. These divisions cut the original cell perpendicularly and determine the appearance of polyhedral cells. Some more fissures develop irregularly, dividing the spores already formed so that they become still smaller and more irregular. Finally these spores become circular.

De Almeida stated that he had found descriptions of similar spherical bodies in the reports of Rixford and Gilchrist [2b] and Posadas and that he could see no justification for considering that these bodies represent a different species from C. immitis.

In our series we have found the usual type of endosporulating spherules and the types just described lying side by side, having developed from the same chlamydospore mixture (fig. 4*a* to *c*). We are unable to say why some of the spherules develop in one way and some in another. However, we are convinced that they do not represent different species of Coccidioides but are variations in development due to some unexplained environmental factor.

Another phenomenon that was first described by Posadas [15] and subsequently by Ophüls [4a] is the development of a cluster of smaller spherules within the capsule of a mother spherule that has not ruptured. Posadas described these as vegetative forms: "The vegetative form begins with the appearance in the protoplasm of the parasite which is going to divide of small clear spherules which slowly become formed into adult endocysts that are retained within the mother cyst." Ophüls disagreed that a different type was indicated and said that they signify very rapid development: "Sometimes, at least in my first case, the

17. de Almeida, F. P.: Considérations sur les genres Coccidioides immitis et Pseudococcidioides Mazzai, Compt. rend. Soc. de biol. **110**:137, 1932.

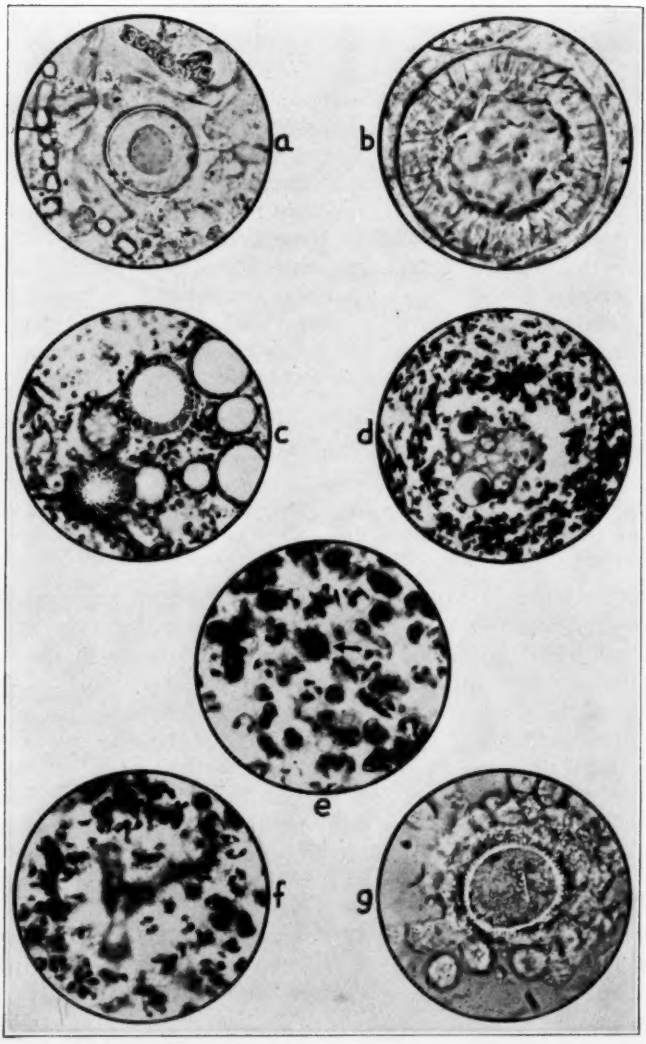

Fig. 4.—Section *a* shows a vacuolated spherule and the partly differentiated mycelium forty-four hours after injection; *b*, the beginning formation of endospores in a vacuolated spherule (see Mazzai's description); *c*, two types of endosporulation from the same mycelial mixture (the upper one corresponds to Rixford's C. pyogenes); *d*, a clump of spherules formed within an unruptured mother spherule; *e*, a minute, burrlike body with fine spicules, found in the depths of a collection of pus; *f*, a fragment of mycelium showing fine spicules, and *g*, a normal-sized spherule with marked prickle formation.

development of the young forms from the spores takes place within the old membrane. This seems to occur when the development of the parasite is an especially rapid one. The young forms certainly develop into the larger forms by simple enlargement."

We occasionally have observed such clusters in sections of tissue (fig. 4*d*). On occasion we have seen spherules in pus in which the diameter was perhaps double that of the usual size and which were filled with small spherules several times the diameter of the usual endospore. In one series of sections in bovine coccidioidal granuloma these clusters were more frequent than we have observed elsewhere, but we have seen them also in the testicle of a guinea-pig eight days after the injection of fungus into the testicle. No explanation for them is apparent.

Another unusual form was first described by Rixford,[2a] who stated that he found prickles on the capsules of a very few of the hundreds of spherules which he examined. Ophüls [4b] reported that short prickles are almost constant on the outside of sporulating forms, Wohlbach [6] described them on young spherules developing from mycelia and Ahlfeldt [8b] stated that they are "found only on the adult forms when they are ready to liberate the young forms."

Our observations coincide more closely with those of Wohlbach. In one series of animals in which intraperitoneal injections were given, abscesses in the epididymis showed minute circular bodies, no larger than an erythrocyte, which were completely surrounded by fine radiating spicules which produced a "burr-like" appearance (fig. 4*e*). These occurred in the depths of collections of pus cells and were not seen elsewhere. In the same sections were seen smooth spherules which did not contain spores but were of average size and were distributed in areas at the edge of the collection of pus cells. These large spherules did not show prickle formation. From our study of tissues, which will be reported later, it is apparent that mature spherules do not usually develop within the dense accumulations of pus but around their margins, so that it may be that these small prickly organisms are the result of an unfavorable environment, due either to insufficient oxygenation or to the toxins which caused the accumulation of the pus.

Prickle formation was observed also in some chains of chlamydospores which had not yet separated sixty hours after they were injected (fig. 4*f*) and in mature nonsporulating spherules (fig. 4*g*), apparently similar forms to those described by Wohlbach. No definite prickle formation was ordinarily observed on endosporulating spherules, although it was present on rare occasions. Figure 4 shows examples of these various bizarre forms.

The various phases of development of the fungus on culture medium and in the tissues correspond, therefore, on the whole, with those that have been described by previous investigators. They are described here because it seemed advisable to check the various stages of development and to have a clearly cut picture of how the fungus acts, before attempting to ascertain the type of tissue reactions which are caused by it. A study of the manner in which the fungus produces lesions and spreads within the body will be published in a later report.

SUMMARY

Clinical observations are narrated to show that the accepted description of coccidioidal granuloma is that of the advanced or terminal stages of an infection which has not often been recognized during the acute stage.

Proof that primary infection may follow the inhalation of the chlamydospores of Coccidioides with the development of bronchopneumonia and erythema nodosum has been given.

A review of the literature concerning the various phases of development of Coccidioides in the vegetative form and in the parasitic state has been given, and experimental evidence has been described to aid in evaluating previous work.

This report is preliminary to a description of how this fungus acts within the animal tissue.

SERUM PHOSPHATASE IN JAUNDICE

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Since Roberts [1] first reported an increase in the phosphatase content of the serum of certain patients with obstructive jaundice, this phenomenon has attracted considerable attention. There still appears to be some difference of opinion regarding the clinical significance of an increase in this factor and its value in differentiating between hepatocellular and obstructive types of jaundice. As this important question can be settled only by the accumulation of observations for large numbers of patients, data obtained for fifty-three patients with jaundice are presented here for the purpose of supplementing those previously reported by other observers.

MATERIAL AND METHODS

The phosphatase content of the serum was determined by the method of Bodansky,[2] blood being withdrawn after a fasting period of about fourteen hours. In our experience, based on determinations made for hospital patients, values below 7 units for adults and 15 units for children are without clinical significance. In thirty-one of the fifty-three patients studied the jaundice was of extrahepatic origin, some form of malignant growth constituting the underlying basis in eighteen instances. In twenty-two patients the jaundice was dependent on conditions commonly regarded as producing icterus of the hepatocellular variety.

RESULTS

The results obtained are presented in the accompanying tables, which include also simultaneous estimations of the bilirubin content of the serum (van den Bergh), the concentration of cholesterol, the urobilinogen content of the urine (Wallace and Diamond) and the bromsul-

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1. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930; Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933.

2. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93, 1933.

phalein retention (thirty minutes after the administration of 2 mg. per kilogram of body weight).

Table 1 comprises thirty-six serum phosphatase determinations for thirty-one patients with obstructive jaundice. All were adults, with the exception of patient 19, an infant of 3 months with congenital obliteration of the bile ducts. The bilirubin concentration of the serum

TABLE 1.—*Serum Phosphatase Values for Patients with Obstructive Jaundice*

Patient Number	Age	Serum Bilirubin, Mg. per 100 Cc.	Bromsulphalein, %	Phosphatase, Units	Urobilinogen: Urine Dilution	Plasma Cholesterol, Mg. per 100 Cc.	Diagnosis
1	59	39.0	100	28.4	Negative	243	Carcinoma of pancreas
		36.0	100	24.6			
2	63	26.0	100	26.0	Negative	263	Carcinoma of pancreas
3	41	26.0	100	12.3	....	...	Stone in common duct
		10.0	100	10.2	1:10	281	
4	42	26.0	100	16.0	Negative	392	Stone in common duct
5	52	24.0	60	21.1	Negative	396	Carcinoma of pancreas
6	58	21.0	100	8.4	Negative	238	Carcinoma of pancreas
7	58	21.0	40	18.1	Negative	206	Carcinoma of pancreas
8	39	7.5	...	14.0	1:10		
		19.5	80	10.0	Negative	•470	Carcinoma of pancreas
9	36	15.2	100	11.0	Negative	1,103	Stricture of common duct
		9.0	70	17.9	Negative	300	
10	44	13.2	80	56.7	1:10	196	Carcinoma of pancreas
11	65	12.0	80	9.8	Negative	336	Stone in common duct
12	52	11.5	50	8.6	1:20	194	Stone in common duct
13	56	11.5	100	20.6	Negative	241	Carcinoma of liver
14	54	11.2	80	8.7	Negative	...	Carcinoma of ampulla
15	57	10.7	60	7.0	Negative	256	Carcinoma of pancreas
16	29	10.4	100	21.3	Negative	264	Stricture of common duct
17	70	10.2	100	23.7	Negative	192	Stone in common duct
18	53	10.0	100	6.2	1:40	232	Carcinoma of pancreas
19	3 mo.	18.3	100	7.2	Negative	340	Congenital obliteration of bile ducts
20	39	7.4	50	21.3	1:40	570	Carcinoma of pancreas
21	32	7.3	80	20.8	....	248	Stone in common duct
22	48	7.2	40	24.7	1:10		
		9.6	80	22.1	Negative	548	Carcinoma of liver
23	60	6.9	20	8.4	1:100	302	Carcinoma of pancreas
24	49	6.4	100	35.0	Negative	408	Carcinoma of pancreas
25	27	6.4	10	11.1	1:10	168	Lymphosarcoma
26	55	6.4	80	24.7	Negative	135	Stone in common duct
27	73	5.4	50	10.6	1:10	...	Pancreatitis
28	73	4.8	80	17.1	1:10	...	Carcinoma of pancreas
29	60	4.5	50	9.2	1:20	...	Carcinoma of pancreas
30	50	4.4	100	7.9	1:10	232	Stone in common duct
31	56	2.2	60	10.9	1:20	241	Stone in common duct

ranged from 2.2 to 39 mg. per hundred cubic centimeters and the phosphatase content from 6.2 to 56.7 units per hundred cubic centimeters.

Table 2 comprises twenty-four phosphatase determinations for 22 patients with jaundice of hepatocellular origin. The bilirubin concentration of the serum ranged from 0.6 to 13.8 mg. and the phosphatase content from 4.9 to 24.5 units per hundred cubic centimeters.

The data presented in table 3 indicate the distribution of the phosphatase values for the two groups of patients. The patients with obstructive jaundice are divided into two groups, because of the report

by some observers of an increase in phosphatase activity in association with malignant neoplastic disease and because of the usually progressive and persistent character of the jaundice in such cases as contrasted with jaundice due to calculous obstruction of the common duct.

TABLE 2.—*Serum Phosphatase in Hepatocellular Jaundice*

Patient Number	Age	Serum Bilirubin, Mg. per 100 Cc.	Bromsulphalein, %	Phosphatase, Units	Urobilinogen: Urine Dilution	Plasma Cholesterol, Mg. per 100 Cc.	Diagnosis
32	69	13.8	100	4.9			
		1.5	60	6.8	1:60	115	Cholecystitis
		0.6	15	5.8			
33	26	13.5	20	11.5	1:40	122	Catarrhal jaundice
34	34	11.4	100	14.9	1:100	156	Cholecystitis
35	30	10.4	80	21.0	1:200	102	Arsphenamine hepatitis
36	48	9.8	100	9.9	1:40	245	Arsphenamine hepatitis
37	48	9.8	90	6.8	1:100	104	Portal cirrhosis
38	22	8.8	80	8.7	1:400	90	Catarrhal jaundice
39	18	8.7	30	7.0	1:100	95	Banti's disease
40	34	8.2	100	12.0	1:200	98	Catarrhal jaundice
41	14	7.2	80	12.3	1:200	110	Catarrhal jaundice
42	40	7.2	30	5.4	1:100	140	Cholecystitis
43	59	7.1	50	6.4	1:80	146	Carcinoma of liver; no obstruction
44	14	6.9	30	23.2	1:100	224	Splenic anemia
45	34	6.8	80	5.2	1:100	130	Hepatitis
46	57	5.8	100	12.2	1:100	100	Hepatitis
47	25	5.6	60	9.4	1:40	162	Cholecystitis
48	35	4.8	80	9.4	1:200	128	Catarrhal jaundice
49	56	4.8	60	15.2	1:80	142	Portal cirrhosis
50	67	4.2	15	12.6	1:20	184	Syphilis of liver
51	69	3.8	15	7.2	1:60	192	Cholecystitis
52	59	1.5	90	24.5	1:200	105	Cholecystitis
53	24	1.4	20	7.9	1:40	117	Hepatitis

TABLE 3.—*Distribution of Phosphatase Values for Thirty-One Patients with Obstructive and Twenty-Two Patients with Hepatocellular Jaundice*

	Number of Values Falling Within the Range			
	0 to 10 Units	10 to 20 Units	20 to 30 Units	Over 30 Units
Nonmalignant obstruction	4	4	5	0
Malignant obstruction	6	4	6	2
Total obstruction	10	8	11	2
Hepatocellular jaundice	12	7	3	0

COMMENT

These data are essentially in agreement with those reported by Bodansky and Jaffe;[3] Herbert,[4] and Greene, Shattuck and Kaplowitz.[5]

3. Bodansky, A., and Jaffe, H. L.: (*a*) Phosphatase Studies: IV. Serum Phosphatase of Non-Osseous Origin; Significance of the Variations of Serum Phosphatase in Jaundice, Proc. Soc. Exper. Biol. & Med. **31**:107, 1933; (*b*) Phosphatase Studies: VIII. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, ibid. **31**:1179, 1934.

4. Herbert, F. K.: Plasma Phosphatase in the Various Types of Jaundice, Brit. J. Exper. Path. **16**:365, 1935.

5. Greene, C. H.; Shattuck, H. F., and Kaplowitz, L.: The Phosphatase Content of the Blood Serum in Jaundice, J. Clin. Investigation **13**:1079, 1934.

As in the case of the data presented by Greene and his colleagues, the phosphatase values obtained in the present series exhibit a wide overlapping in obstructive and hepatocellular jaundice. This observation is contradictory to the findings of Roberts [1] and Rothman, Meranze and Meranze,[6] who said they believed that there is a rather sharp line of demarcation in this regard between these two types of jaundice. Rothman and his associates found values greater than 10 units per hundred cubic centimeters (modified Roberts method) for twenty-five of twenty-nine patients with obstructive jaundice and 10 units or less for eighteen of twenty-four with hepatocellular jaundice. Although the data reported by practically all investigators of this problem indicate that a larger proportion of patients with obstructive than of those with hepatocellular jaundice exhibit very high phosphatase values, it appears that the

TABLE 4.—*Distribution of Phosphatase Values for Fifty Patients with Obstructive and Forty-One with Hepatocellular Jaundice (Combined Data of Present Series and That of Greene, Shattuck and Kaplowitz)*

	Number of Values Falling Within the Range			
	0 to 10 Units	10 to 20 Units	20 to 30 Units	Over 30 Units
Nonmalignant obstruction	5	10	6	4
Malignant obstruction	7	5	9	4
Total obstruction	12	15	15	8
Hepatocellular jaundice	15	16	7	3

relatively sharp delimitation of these values in the groups of patients studied by Roberts [1] and Rothman, Meranze and Meranze [6] is purely coincidental. Unfortunately the difference in the methods employed by different observers renders impossible a quantitative correlation of all the reported observations.

Table 4 comprises the combined data of the present series and that of Greene, Shattuck and Kaplowitz [5] obtained by the same method (Bodansky). Comparison with table 3 indicates clearly the alteration in distribution of phosphatase values when the influence of chance is lessened by increasing the number of observations. It is noted that the value for serum phosphatase was below 10 units in 24 per cent of fifty patients with obstructive and in 36.6 per cent of forty-one with hepatocellular jaundice. In view of this fact, the observation that values above 20 units were obtained in 46 per cent of those with obstructive jaundice and in only 24.4 per cent of those with hepatocellular jaundice has little if any practical significance from the standpoint of differential diagnosis.

6. Rothman, M. M.; Meranze, D. R., and Meranze, T.: Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice, Am. J. M. Sc. **192**:526, 1936.

As has been found by previous investigators, there was no close correlation between the degree of bilirubinemia and the phosphatase level for either group of patients. This lack of relationship is well illustrated by patients 6, 19, 20, 22, 24, 26, 32 and 52. It is interesting in this connection to note that for a patient with portal cirrhosis studied by Greene and his associates [5] the bilirubin content of the serum was 30.5 mg. per hundred cubic centimeters and the phosphatase content was 1.3 units, whereas for another the phosphatase content was 19.9 units and the bilirubin content was within normal limits.

In the cases reported by Herbert,[4] although there was no close correlation between the duration of jaundice and the level of serum phosphatase, very high values were more frequent in cases of malignant growth than in cases of calculous obstruction. It was suggested that recent, incomplete or intermittent obstruction may be associated with relatively slight increases in the phosphatase content. However, when our data are combined with those of Greene, Shattuck and Kaplowitz,[5] there appears to be little significant difference in distribution for patients with malignant and those with nonmalignant obstructive jaundice. Furthermore, the serum phosphatase was normal in patient 19, an infant of 3 months with congenital obliteration of the bile ducts. These observations appear to indicate the lack of influence of duration and permanence of obstruction in this connection. However, it must be borne in mind that, as pointed out by Bodansky and Jaffe,[3a] anemia, malnutrition and senility tend to lower the phosphatase content of the serum and should be taken into consideration in interpreting clinical variations in this factor.

It seems futile in the present state of knowledge to theorize regarding the possible mechanism of production of the increase in serum phosphatase in jaundice of obstructive and hepatocellular origin. The subject has been reviewed recently by Herbert [4] and one of us (A. C.).[7] It appears to be clear, however, that this increase cannot be explained, as Herbert implied, on the basis of obstruction to the flow of bile, either extrahepatic or intrahepatic. This hypothesis is contradicted by observations, such as those of Greene and his colleagues [5] in portal cirrhosis, just cited, and by the data for patient 52 in the present series, which showed marked elevation of the phosphatase level accompanied with little or no increase in serum bilirubin. The presence of normal phosphatase activity in an infant of 3 months with congenital obliteration of the bile ducts appears to be incompatible with such a hypothesis. Further-

7. Cantarow, A.: Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, Internat. Clin. **1**:230, 1936.

more, Stewart, McCool and one of us (A. C.)[8] found little or no increase in the phosphatase content in a large series of cats with total biliary stasis of varying duration produced by ligation of the common bile duct. This observation is interesting because of the marked increase which was noted under such circumstances in dogs by Bodansky and Jaffe[3b] and Armstrong and King.[9] It seems unlikely that there would be so marked a species difference in this respect if stasis per se were the only etiologic factor of fundamental importance. It should be noted also that Hartman and Schelling[10] and Armstrong and King[9] found an increase in serum phosphatase in dogs in the presence of hepatic functional impairment produced by a variety of methods (modified Eck fistula, high voltage roentgen irradiation, carbon tetrachloride, chloroform, phosphorus and toluylenediamine).

The data obtained for the present series of patients support the view that determination of the level of serum phosphatase is of no value in distinguishing jaundice of obstructive from that of hepatocellular origin.

SUMMARY

Serum phosphatase determinations were obtained for thirty-one patients with obstructive and twenty-two with hepatocellular jaundice. There was a wide overlapping of phosphatase values in the two groups, which became even more pronounced when the present data were combined with those reported by other observers employing the same methods. It appears that this procedure is of no value in differentiating between these two types of jaundice.

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8. Cantarow, A.; Stewart, H. L., and McCool, S. G.: Serum Phosphatase in Cats with Total Bile Stasis, Proc. Soc. Exper. Biol. & Med. **35**:87 (Oct.) 1936.

9. Armstrong, A. R., and King, E. J.: Serum Phosphatase in Toxic and Haemolytic Jaundice, Canad. M. A. J. **32**:379, 1935.

10. Hartman, F. W., and Schelling, V.: Serum Phosphatase in Experimental Insufficiency of the Liver, Arch. Path. **18**:594 (Oct.) 1934.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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PERNICIOUS ANEMIA

ETIOLOGY

The mechanism of the development of pernicious anemia has been explained by Castle [1] on the basis of interaction of an "intrinsic factor" secreted by the gastric mucosa and an "extrinsic factor" provided by the diet, thereby producing a substance which controls the maturation of red blood cells in the bone marrow. Greenspon [2] has performed experiments which in his opinion suggest a different interpretation of the observations of Castle. Greenspon's theory is as follows: It is assumed that an erythrocyte-stimulating hormone is secreted by the gastric mucosa. When pernicious anemia develops there is a loss of this hormone, coincident with atrophy of the gastric glands, and the anemia of the disease develops. In support of his theory this investigator reported that the injection of extracts of gastric mucosa of the hog into rabbits and guinea-pigs caused (1) a substantial increase in the number of circulating erythrocytes, (2) moderate reticulocytosis and (3) hyperplasia of the bone marrow. Certain other experiments were performed which led to the conclusion that the addition of pepsin destroys the antianemic properties of stomach U. S. P. In addition, the author

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The present review deals with the literature on hematology which appeared in 1936. A few articles which were published in 1935 are included. To conserve space it has been necessary to select certain papers at the expense of others. A number of the more important contributions which have been omitted will be included in subsequent reviews.

1. Castle, W. B.: The Etiology of Pernicious and Related Macrocytic Anemias, Science **82**:159 (Aug. 23) 1935.

2. Greenspon, E. A.: The Nature of the Antipernicious Anemia Principle in Stomach: Method to Improve Stomach Preparations, J. A. M. A. **106**:266 (Jan. 25) 1936.

concluded that the oral administration of gastric juice alone is effective if peptic activity is prevented. This is contrary to the basic experiments of Castle and his co-workers. Greenspon's theory, which places a different interpretation on the experiments of Castle relating to the interaction of an intrinsic factor and beef muscle (extrinsic factor), may be stated as follows: Normal gastric juice contains an antianemic factor and free pepsin. The pepsin has an "antagonistic" action toward the antianemic factor and renders it inert. When gastric juice is incubated with beef muscle, the protein of the muscle interacts with the free pepsin to form bound pepsin, thereby permitting the antianemic factor to become active. From the experiments performed and certain theoretical considerations, a new method of making stomach preparations was suggested in which the antagonistic action of pepsin was eliminated.

Hanes, Hansen-Prüss and Edwards [3] repeated some of Greenspon's experiments, adhering strictly to his technic, with negative results. Greenspon had reported that "the oral administration of normal gastric juice is effective in pernicious anemia if peptic activity is prevented; also that the mere physical presence of pepsin is not destructive to the anti-pernicious factor, if the pepsin is inactive." Hanes and his colleagues fed gastric juice, modified by the technic of Greenspon, to 5 patients with pernicious anemia and did not observe any subjective or objective evidence of improvement in the condition of the patients. Other experimental data which are not in accord with Greenspon's theory have been reported by Flood and West,[4] Ungley [5] and Moffett and Fitz-Hugh and Creskoff.[6]

Castle and Ham [7] in a direct reply to Greenspon cited a group of experiments which "fail to sustain" Greenspon's conclusion. Their observations led to the following conclusions:

1. Normal human gastric juice does not contain, on oral administration, an "antipernicious anemia principle" effective without contact with food (extrinsic factor).

3. Hanes, F. M.; Hansen-Prüss, O. C., and Edwards, J. W.: The Feeding of Modified Gastric Juice in Pernicious Anemia, J. A. M. A. **106**:2058 (June 13) 1936.

4. Flood, C. A., and West, R.: Some Properties of Castle's Intrinsic Factor, Proc. Soc. Exper. Biol. & Med. **34**:542, 1936.

5. Ungley, C. C.: Observations on Castle's Intrinsic Factor in Pernicious Anaemia, Lancet **1**:1232 (May 30) 1936.

6. Fitz-Hugh, T., Jr., and Creskoff, A. J.: Experiments with "Depepsinized" Human Gastric Juice in Treatment of Pernicious Anemia, Am. J. M. Sc. **192**: 168, 1936.

7. Castle, W. B., and Ham, T. H.: Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia: Further Evidence for the Essential Participation of Extrinsic Factor in Hematopoietic Responses to Mixtures of Beef Muscle and Gastric Juice and to Hog Stomach Mucosa, J. A. M. A. **107**:1456 (Oct. 31) 1936.

2. Mucosa of hog stomach contains both a thermostable (extrinsic) factor and a thermolabile (intrinsic) factor presumably responsible for the activity of such mucosa and of whole desiccated hog stomach.

3. Incubation of normal human gastric juice for two hours at 37.5 C. in the presence of native pepsin and hydrochloric acid inactivates only a portion of its content of intrinsic factor.

4. Beef muscle (extrinsic factor) and gastric juice (intrinsic factor) administered without opportunity for contact are not effective in pernicious anemia.

Ever since liver therapy has been used in the treatment of pernicious anemia, attempts have been made by various investigators to isolate the active antianemic principle from that substance. In 1935 Dakin and West described the preparation and partial purification of a product from liver which was effective in causing regeneration of blood in pernicious anemia. In 1936 Dakin, Ungley and West [8] reported further studies on the isolation of this substance and recorded certain conclusions which may be deduced from the chemical data thus acquired. They confirmed their previous observation that the active principle in liver is, or is associated with, a peptide which possesses some of the properties of an albumose. Additional studies indicated that an aminohexose (dextrosamine) is not an essential part of the molecule. On hydrolysis the peptide yields arginine, leucine, amino-acetic acid, proline, hydroxyproline, aspartic acid and an acid resembling hydroxyglutamic acid. Their work indicated that the substance has a molecular size of about 2.1 millimicrons and a molecular weight between 2,000 and 5,000. When the methods of isolating this material are applied to kidney and brain, they do not yield a hematopoietic substance.

Of interest from the standpoint of the relation of gastric juice to the etiology of pernicious anemia are the experiments of Mermod.[9] This investigator, following the method of Jacobson,[10] demonstrated that an increase in the number of reticulocytes in the peripheral blood of guinea-pigs followed the intraperitoneal injection of congo red and the intravenous injection of gastric juice from normal subjects and those having gastric anacidity but no anemia. The intramuscular injection of gastric juice from patients with pernicious anemia was not followed by an increase in the reticulocyte count of guinea-pigs within

8. Dakin, H. D.; Ungley, C. C., and West, R.: Further Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, J. Biol. Chem. **115**:771, 1936.

9. Mermod, C.: Reticulocytosis in Guinea Pig Following Injections of Gastric Juice and Congo Red, J. Clin. Investigation **15**:559, 1936.

10. Jacobson, B. M.: Note on Guinea-Pig Method of Assay of Liver Extract, Brit. J. Exper. Path. **17**:307, 1936.

the first eight days. The reaction of the guinea-pig to the intramuscular injection of gastric juice was proposed as a test for the diagnosis of anemia of obscure origin. Such data could be interpreted as further evidence that the fundamental defect in pernicious anemia is in the gastric secretions. The failure of Jacobson's method of studying reticulocytogenic substances to receive unanimous confirmation causes one to withhold complete acceptance of Mermod's work until additional studies have been made.

Cheney [11] incubated scrapings of human duodenal mucosa with liver and liver extract and administered the resultant substance to patients with pernicious anemia and other macrocytic anemias. He concluded that a "duodenal ferment" increases the efficacy of liver as a therapeutic agent in these types of anemia. He considered that the "unknown ferment" ("intrinsic factor" of Castle) is at a higher concentration in the duodenal mucosa than in the stomach and that in patients with pernicious anemia there is a gastroduodenal defect or an inactivity of the pyloric region (Brunner's gland). He suggested that the activity of the duodenal mucosa explains the absence of macrocytic anemia in some patients with gastric achylia and atrophy of the mucosa of the stomach and also may account for the failure of this type of anemia to follow gastrectomy in all instances.

Goldhamer [12] studied the volume of gastric juice of 26 patients during a relapse of pernicious anemia. The average volume secreted per hour was 20 cc., as compared with the normal secretion, which is about 150 cc. per hour. When this material was incubated with beefsteak and fed to other patients during a relapse, a reticulocyte response was observed. It was concluded from these experiments that in patients with pernicious anemia the intrinsic factor was present in the stomach contents but that the deficiency was quantitative rather than qualitative. Palmer and Porter [13] and Fitz-Hugh and Creskoff [6] performed similar experiments but were unable to confirm this work.

The relationship of the functions of the stomach to the production of red blood cells is not limited to pernicious anemia. Naegeli [14] pointed out that many anemias may result from deficiencies of the stomach and gastro-intestinal tract but that liver and desiccated stomach are of value

11. Cheney, G.: Investigation into Production of Proteolytic Ferment in Duodenum Which Will Increase Anti-Anemic Efficacy of Liver: Its Relationship to Cause of Pernicious Anemia, Am. J. Digest. Dis. & Nutrition **3**:541, 1936.

12. Goldhamer, S. M.: Presence of Intrinsic Factor of Castle in Gastric Juice of Patients with Pernicious Anemia, Am. J. M. Sc. **191**:405, 1936.

13. Palmer, W. L., and Porter, R. T.: Combined Cord Degeneration Without Anemia: A Case Report with Studies Bearing on the "Intrinsic Factor" of Castle, J. Clin. Investigation **15**:343, 1936.

14. Naegeli, O.: Die Beziehungen des Magen-Darmkanals zur Blutbildung und zur Entstehung von Anämien, Helvet. med. acta **3**:581, 1936.

only in pernicious anemia. It is shown by Apperly and Cary [15] that there is a direct relationship between the red cell count of peripheral blood and the degree of gastric acidity. In anemia due to hemorrhage, if more than one third of the total red blood cells are lost "free" acid disappears from the stomach content. As the blood approaches normal, the "free acid" returns, and the amount gradually approaches normal. In polycythemia the acidity again falls. The latter observation is contrary to the beliefs of some investigators, who are of the opinion that the increased production of red blood cells in polycythemia is the result of overactivity of gastric secretion. Apperly [16] pointed out that when anemia is associated with achlorhydria, it is necessary to distinguish between "achlorhydric" anemia and the absence of "free" acid as a result of a reduced number of red cells in the peripheral blood.

In studying the anemias of children Racugno [17] stated that many of them can be differentiated by careful studies of the gastric chemistry. In his opinion the gastric changes are secondary to the existing anemia.

Several interesting observations were reported by Karczag,[18] who made spectographic studies of the gastric contents of patients with pernicious anemia. He pointed out that the gastric secretions have a selective absorption spectrum and that the values obtained for patients with pernicious anemia are quantitatively lower but similar in type to those of normal persons. The gastric juice is not a protein, polypeptide, aromatic amino-acid, lactic acid or bile pigment but resembles the vitamin B complex.

SYMPTOMATOLOGY, CHANGES IN THE BLOOD AND MANIFESTATIONS DUE TO LESIONS IN THE SPINAL CORD AND BRAIN

An analysis of 580 consecutive cases of true pernicious anemia was reported by Isaacs.[19] From the data a patient with pernicious anemia is defined statistically as a man or woman (equal possibility) between the ages of 35 and 55 years, of no specific nationality but generally of a race originating in the northern European countries, who is underweight, who has light-colored hair, generally blue eyes and pale skin, and long wide ears, and who shows no secretion of hydrochloric acid

15. Apperly, F. L., and Cary, M. K.: Relation of Gastric Acidity to Erythrocyte Content of Blood, Am. J. Digest. Dis. & Nutrition **3**:466, 1936.

16. Apperly, F. L.: Gastric Acidity and Its Significance: Clinical and Experimental Study, Lancet **1**:5 (Jan. 4) 1936.

17. Racugno, A.: Osservazioni intorno alle conoscenze sul chimismo gastrico nei bambini, Clin. pediat. **18**:129 and 331, 1936.

18. Karczag, L.: The Spectrographic Anomalies of Gastric Juice in Pernicious Anaemia, Lancet **1**:947 (April 25) 1936.

19. Isaacs, R.: Blood Cell Morphology in Constitutional Types and Heredity, in Medical Papers Dedicated to H. A. Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc., 1936, p. 538.

at any time in the stomach; relative hypotension; a tendency to hyperchromic macrocytic anemia, leukopenia and hyperbilirubinemia; atrophy of the lingual papillae, and neurologic changes associated with lesions in the posterolateral columns of the spinal cord.

In Hoffmann's [20] series of 57 patients the total number of leukocytes varied from 2,000 to 3,500 per cubic millimeter. There was an initial increase after liver therapy or blood transfusion. In half the patients who received liver therapy the improvement in the leukocyte picture did not appear until after there was a response of the red blood cells, after which the "shift to the right" of the polymorphonuclears, the relative lymphocytosis and the monocytopenia were replaced by a more normal condition. Eosinophilia, however, frequently persisted. In half the cases the rapid improvement in the leukocyte picture was of prognostic value.

Reichel [21] noted that the speed of sedimentation of the red blood corpuscles is increased when the anemia is marked and that it decreases as the blood count improves.

Van der Sande [22] described a condition noted by others, namely, the development of carcinoma of the stomach in patients with pernicious anemia. The patients fall into the proper age group and would naturally be susceptible to the development of a neoplasm. So far no definite relationship between the two diseases has been established. It is wise to think of the possibility of a gastric neoplasm in patients under treatment for pernicious anemia. Among diseases and syndromes which have been described in association with pernicious anemia are hyperthyroidism (Andrus and Wintrobe [23]); diabetes mellitus, terminating in acute myeloid leukemia (Elman and Marshall [24]); myxedema (Holbøll [25] and Greene [26]), and bacillary dysentery (Greene [27]).

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20. Hoffmann, D.: Beobachtungen über das Verhalten des weissen Blutbildes bei perniziöser Anämie in der Zeit vor und nach Einführung der Lebertherapie, Klin. Wchnschr. **15**:598 (April 25) 1936.

21. Reichel, H.: Blutkörperchensenkung bei perniziöser Anämie, Klin. Wchnschr. **14**:1679 (Nov. 23) 1935.

22. van der Sande, D.: Question of Relation Between Pernicious Anemia and Gastric Cancer, Nederl. tijdschr. v. geneesk. **80**:4774 (Oct. 24) 1936.

23. Andrus, E. C., and Wintrobe, M. M.: Note upon the Association of Hyperthyroidism and Pernicious Anaemia, Bull. Johns Hopkins Hosp. **59**:291, 1936.

24. Elman, C., and Marshall, S.: Anaemia of Pernicious Type Complicated by Diabetes Mellitus and Terminating in Acute Myeloid Leukaemia, Lancet **2**: 1094 (Nov. 7) 1936.

25. Holbøll, S. A.: Anaemia perniciosa og myxødem, Hospitalstid. **78**:1181 (Nov. 12) 1935.

26. Greene, J. A.: Comparison of Symptoms, Physical and Laboratory Findings of Myxedema and Pernicious Anemia, with Report of Three Cases, Ann. Int. Med. **10**:622, 1936.

27. Greene, J. A.: Diagnosis of Bacillary Dysentery: Report of a Chronic Case Associated with Pernicious Anemia, J. Iowa M. Soc. **26**:148, 1936.

Patients with pernicious anemia may first present themselves to the physician for relief of the neurologic symptoms. Of Craig's [28] series, 12.7 per cent of the patients with pernicious anemia had a neurologic complication as the main symptom: paresthesias, 80 per cent; girdle pain, 2.8 per cent, and sensation of a tight band around the knees, 1.7 per cent. In 1.4 per cent of the patients the nervous manifestations antedated the appearance of the anemia. Among other authors reporting carcinoma of the stomach and pernicious anemia are Calabresi; [29] Greyman, Livshits and Pevzner; [30] Grill; [31] Rambach; [32] Silverman,[33] and Thiele.[34]

The extremely common occurrence of symptoms and signs referable to the central nervous system in pernicious anemia has led most investigators to the conclusion that it is a part of the same disease process. The opinion has been expressed that if neurologic complications are absent in a case of macrocytic anemia, although pernicious anemia is a possibility, one should look for other causes of macrocytic anemia. The etiology of the changes in the nervous system remains obscure. It is believed by some that the manifestations in the spinal cord may result from a vitamin deficiency. Others still maintain that there is a specific neurotoxin due to a disturbance in lipid metabolism or that the changes in the central nervous system are related directly to the anemia. There is considerable opposition to the latter view. Palmer and Porter [13] have reported a case of combined degeneration of the spinal cord without any evidence of anemia.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, ataxia, loss of finer coordination of the fingers and disturbances of the bowel and bladder. The character of the signs depends on the site of the lesion and the extent of the patho-

28. Craig, W. M.: Tumors of the Spinal Cord and Their Relation to Medicine and Surgery, J. A. M. A. **107**:184 (July 18) 1936.

29. Calabresi, M.: Anemia perniciosa e carcinoma gastrico, Policlinico (sez. prat.) **43**:1685 (Sept. 21) 1936.

30. Greyman, A. A.; Livshits, S. M., and Pevzner, S. D.: Malignant Degeneration of Gastric Adenoma Associated with Pernicious Anemia, Vestnik. khir. **45**: 245, 1936.

31. Grill, H.: Ein Fall von Anaemia perniciosa und Magencarcinom, Folia haemat. **54**:410, 1936.

32. Rambach, H.: Ueber die Entwicklung von Magenkrebs bei der perniziösen Anämie, Monatschr. f. Krebsbekämpf. **4**:201, 1936.

33. Silverman, S.: Pernicious Anaemia Followed by Carcinoma of the Stomach, Lancet **2**:71 (July 11) 1936.

34. Thiele, W.: Perniziöse Anämie und Magencarcinom unter besonderer Berücksichtigung ihres familiären Auftretens, Klin. Wchnschr. **15**:921 (June 27) 1936.

logic involvement of the spinal cord. Tourreilles and Vázquez [35] pointed out that the anterior, lateral or posterior gray columns of the cord may be involved separately or simultaneously. As a result the reflexes may be increased, decreased or absent. The mental picture is not specific, and many observers are of the opinion that the manifestations of cerebral involvement are independent of the disease process of pernicious anemia. Schwab and Schwab [36] discussed the association of pernicious anemia and the parkinsonian syndrome and discussed the possible etiology.

The neurologic and psychiatric features have been emphasized by Cain and Ceillier; [37] Cain, Ceillier, Cattan and Bachman; [38] Langelüddeke,[39] and Petit and Delmond.[40]

TREATMENT

After the use of liver extract made by the method of Dakin and West, improvement in the blood of patients with pernicious anemia was noted by Ungley, Davidson and Wayne [41] and also by Wilkinson.[42] In 11 patients doses of from 1 to 6 cc. (100 to 600 mg.) caused an increase in the red blood cell count in forty days, but larger doses were required for the production of red blood cells at a maximal rate. The results demonstrate that the Reinecke acid extraction of liver separates a considerable amount of the hematopoietically active principle.

Murphy [43] recommended the intramuscular injection of liver extract as the method of choice in the treatment of pernicious anemia. He

35. Tourreilles, J. F., and Vázquez, P. C.: Neuro-Anemic Syndrome of Unusual Localization, Semana méd. **2**:1583 (Dec. 3) 1936.

36. Schwab, S. I., and Schwab, R. S.: Pernicious Anemia and Combined System Disease with Diabetes Mellitus and Parkinsonian Syndrome: Report of Case, Arch. Neurol. & Psychiat. **35**:126 (Jan.) 1936.

37. Cain, A., and Ceillier, A.: Contribution à l'étude des psychoanémies. Examen psychiatrique de quatre cas d'anémie de Biermer, Ann. méd.-psychol. (pt. 1) **94**:582, 1936.

38. Cain, A.; Ceillier, A.; Cattan, R., and Bachman: Anémie biermérienne et troubles psychiques, Sang **10**:770, 1936.

39. Langelüddeke, A.: Ein Fall von perniziöser Anämie mit Psychose und anderen selteneren Symptomen, Deutsche med. Wchnschr. **62**:963 (June 12) 1936.

40. Petit, G., and Delmond, J.: Le syndrome d'Adie en pathologie mentale. Ses rapports avec les syndromes neuro-et psychoanémiques, Ann. méd.-psychol. (pt. 1) **94**:497, 1936.

41. Ungley, C. C.; Davidson, L. S. P., and Wayne, E. J.: Treatment of Pernicious Anaemia with Dakin and West's Liver Fraction (Anahaemin), Lancet **1**:349 (Feb. 15) 1936.

42. Wilkinson, J. F.: Note on Anti-Anaemic Principle of Liver, Lancet **1**: 354 (Feb. 15) 1936.

43. Murphy, W. P.: Treatment of Pernicious Anemia with Intramuscular Injections of Highly Concentrated Solution of Liver Extract, Am. J. M. Sc. **191**:597, 1936.

used a preparation in which 1 cc. was made from 100 Gm. of liver. Injections from every ten to twenty-eight days served to maintain the blood at a normal level.

Autolyzed liver extract was found to be effective by Klumpp [44] in doses of from 1 to 8 teaspoonfuls daily (average 3 teaspoonfuls), representing from 150 to 300 Gm. of liver.

Instead of from 30 to 50 Gm. of dried stomach, Henning and Keilhack [45] used 5 Gm. of a powder made from the mucous membranes of the antrum. For the "extrinsic factor," vegetable protein was used.

Strauss [46] advocated transfusion of blood if there is air hunger or circulatory failure. To anemic patients 10 units of liver extract should be given intramuscularly for three days and then at weekly intervals until the blood count is normal. Larger doses are required to raise the red cell count to 5,000,000 per cubic millimeter. Frequently after twelve months of "normal" blood counts it is possible to increase the interval between injections to two weeks. Strauss advocated large doses of liver extract to arrest completely all progress of degeneration of the spinal cord. "It has been unequivocally established," he said, "that such arrest can be achieved if sufficient amounts of liver extract are employed." This would require 35 units intramuscularly during the first week and at least 10 units a week thereafter and double the dose if the neurologic lesions progress. This treatment must be continued for at least a year and reduced later with great caution. Iron should be added when a hypochromic condition develops. The U. S. P. unit is the amount of material which when given daily will produce a satisfactory rise in the reticulocyte count and an adequate increase in the number of erythrocytes and the percentage of hemoglobin in selected patients with addisonian pernicious anemia.

In the treatment of the neurologic manifestations, Schaller and Newman [47] injected 10 cc. of liver extract intramuscularly once every three weeks, after the initial injections every three or four days for two or three weeks and then at weekly intervals during the first year. In none of their series of 40 patients studied over a period of five years was there any progression of the neural symptoms when adequate treat-

44. Klumpp, T. G.: The Treatment of Pernicious Anemia with Autolyzed Liver Concentrate, J. A. M. A. **106**:1245 (April 11) 1936.

45. Henning, N., and Keilhack, H.: Untersuchungen über eine rationelle Dauertherapie der perniziösen Anämie, Arch. f. Verdauungskr. **59**:129, 1936.

46. Strauss, M. B.: The Pharmacopeia and the Physician: The Use of Drugs in the Treatment of Anemia, J. A. M. A. **107**:1633 (Nov. 14) 1936.

47. Schaller, W. F., and Newman, H. W.: Liver Therapy for Combined Sclerosis, Arch. Int. Med. **58**:45 (July) 1936.

ment was given. If neurologic symptoms do progress, it is a sign that treatment is inadequate.

Baserga [48] recommended injection of liver extract corresponding to 5,000 Gm. a week or in a two week interval for patients with neurologic complications. In his opinion the daily intramuscular injections of liver extract corresponding to 700 Gm. will prevent neurologic symptoms. The hemoglobin value for men should be kept at 100 per cent and that of women at 90 per cent. Large doses of iron and physical reeducation are advocated. It is suggested that discontinuance of therapy because of financial conditions is the main cause of the development of neurologic lesions.

Since there are spontaneous variations in the intensity of the neurologic manifestations without therapy, conclusions drawn from the benefits of specific treatment must be guarded. Improvement in the symptoms and objective arrest of the signs when adequate antianemia therapy is administered have been reported by Haden,[49] Mills [50] and Hyland and Farquharson.[51] Adequate treatment means not only a normal red cell count and hemoglobin value but normal morphologic characteristics of the red blood cells. Russell [52] noted sensory improvement after subcutaneous injections of large doses of vitamin B_1.

A summary of the effects of various types of therapy given to 577 patients with pernicious anemia was given by Sturgis and Isaacs.[53] In this group of patients there were 76 deaths during an eight year period. Thirty-seven, or 49 per cent, died of complications of pernicious anemia, especially lesions associated with changes in the central nervous system. Sturgis [54] stressed the importance of suiting the dose of liver extract to the individual patient.

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48. Baserga, A.: Contributo clinico allo studio delle sindromi nervose dell'anemia perniciosa, Haematologica **17**:603, 1936.

49. Haden, R. L.: The Treatment of the Neuromuscular Sequelae of Pernicious Anemia, S. Clin. North America **16**:1077, 1936.

50. Mills, E. S.: The Effect of Therapy on Nerve Degeneration in Pernicious Anemia, Am. J. M. Sc. **191**:72, 1936.

51. Hyland, H. H., and Farquharson, R. F.: Subacute Combined Degeneration of Spinal Cord in Pernicious Anemia: Results of Treatment in Seventy-Four Consecutive Cases with Certain Clinical Observations, Arch. Neurol. & Psychiat. **36**:1166 (Dec.) 1936.

52. Russell, W. R.: The Parenteral Administration of Vitamin B_1 in the Treatment of Polyneuritis and Other Conditions, Edinburgh M. J. **43**:315, 1936.

53. Sturgis, C. C., and Isaacs, R.: The Present Status of the Treatment of Pernicious Anemia Based on an Experience of Eight Years in Treating Five Hundred and Seventy-Seven Patients, Tr. Am. Clin. & Climatol. A. **51**:28, 1935.

54. Sturgis, C. C.: The Present Status of Pernicious Anemia: Experience with Six Hundred Cases over Eight Years, Ann. Int. Med. **10**:283, 1936.

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA

The various etiologic factors which may produce macrocytic anemia have been discussed in the current reviews of Davidson,[55] Murry [56] and Isaacs and his associates.[57] Although Greenspon [2] suggested that an extrinsic factor was unnecessary, it is generally accepted that the substance required for the normal development of red blood cells is produced by the interaction of the extrinsic and intrinsic factors. The product formed is absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed. If there is a disturbance of any of the factors which are involved in this mechanism, macrocytic anemia will result.

Although the nature of the extrinsic factor has not been identified, Napier [58] and Konstam and Gordon [59] demonstrated clinically that a commercially prepared autolyzed yeast product is a satisfactory source. Any interference with the production of the intrinsic factor by the stomach may produce macrocytic anemia. Bachman [60] reported a case of inflammation of the stomach and macrocytic anemia in an infant less than 1 year of age. Tateno [61] observed the changes in the blood following total gastrectomy in man and suggested the term agastric hypoplastic hyperchromic anemia. Heck and Walters [62] noted a satisfactory response to liver therapy in a woman in whom macrocytic anemia developed after gastric resection.

The macrocytic anemias which have been observed clinically in association with disturbances of gastric function have been difficult to produce experimentally. Bussabarger and Ivy [63] removed the stomachs of 8 monkeys, and microcytic anemia developed in all. Hogs were gas-

55. Davidson, L. S. P.: Pernicious Anaemia and Other Macrocytic Anaemias, Brit. M. J. **1**:804 (April 18) 1936.

56. Murry, H. E.: The Stomach and Anemias, South. M. J. **29**:312, 1936.

57. Isaacs, R.; Sturgis, C. C.; Bethell, F. H., and Goldhamer, S. M.: Blood: A Review of the Recent Literature, Arch. Int. Med. **57**:1186 (June) 1936.

58. Napier, L. E.: Tropical Macrocytic Anaemia, Lancet **2**:679 (Sept. 19) 1936.

59. Konstam, G., and Gordon, H.: Idiopathic Steatorrhea with Skin Lesions and Megalocytic Anaemia, Proc. Roy. Soc. Med. **29**:629, 1936.

60. Bachman, A. L.: Macrocytic Hyperchromic Anemia in Early Infancy: Report of Case and Review of Literature, Am. J. Dis. Child. **52**:633 (Sept.) 1936.

61. Tateno, S.: Ueber 3 Fälle von Totalexstirpation des Magens, insbesondere über deren postoperative Blutbefunde, Arch. f. klin. Chir. **184**:681, 1936.

62. Heck, F. J., and Walters, W.: Development of Macrocytic Anemia Following Resection of Stomach, Proc. Staff Meet., Mayo Clin. **11**:118 (Feb. 19) 1936.

63. Bussabarger, R. A., and Ivy, A. C.: Hematologic Studies on Gastrectomized Monkeys, Proc. Soc. Exper. Biol. & Med. **34**:151, 1936.

trectomized by Bence.[64] During the first year postoperatively microcytic anemia developed, which gradually was replaced by macrocytic anemia. The bone marrow of these animals was similar to that seen in patients with pernicious anemia during a relapse. The stomachs of 45 rats were removed by Bussabarger and Jung,[65] and in all instances hypochromic anemia resulted. This responded best to iron medication plus liver extract. Several investigators gastrectomized dogs. Petri and his co-workers[66] reported normochromatic anemia and also observed degenerative changes in the gray substance of the medulla. Vlados and his colleagues[67] reported the development of both secondary and primary anemia after gastrectomy in dogs. In their opinion the intrinsic factor is a ferment. Fontés and his colleagues,[68] as well as Ducuing and his associates,[69] reported hypochromic anemia following the removal of the stomachs of dogs.

The similarity of the blood picture in patients with pernicious anemia and in those with stricture of the intestine was observed by Faber in 1895. A series of 20 patients with various intestinal lesions associated with anemia has been reported on by Butt and Watkins.[70] Eleven had primary anemia, and the remaining 9 had hypochromic anemia. Hawksley and Meulengracht[71] stated the opinion that the macrocytic anemia which is associated with intestinal strictures is due to impaired absorption or a progressive infection which causes gastritis, followed by atrophy of the gastric mucosa with failure of secretion of the intrinsic factor. Konstam[72] and Konstam and Gordon[59] noted megalocytic

64. Bence, G.: Die Beziehungen der experimentellen agastrischen Anämie zur Perniciosa, Ztschr. f. klin. Med. **130**:275, 1936.

65. Bussabarger, R. A., and Jung, F. T.: Dietary and Hematologic Studies After Gastrectomy in the Rat, Am. J. Physiol. **117**:59, 1936.

66. Petri, S.; Bøggild, D., and Ohlsen, A. S.: Experimental Investigations on Gastrogenic Anemias (in Dogs): Results of Operative Removal Either of Whole Stomach Plus Brunner Gland Region in Duodenum, or of Fundus Region Only, Hospitalstid. **79**:509 (May 19) 1936.

67. Vlados, H.; Bagdasarov, A.; Dulcin, M., and Bondarenko, E.: The Part Taken by the Stomach in the Regulation of Blood-Formation, Acta med. Scandinav. **88**:295, 1936.

68. Fontés, G.; Kunlin, J., and Thivolle, L.: Le métabolisme du fer et l'hématopoïèse chez le chien après gastrectomie totale et exclusive, Sang **10**: 433, 1936.

69. Ducuing, J.; Miletzky, O., and Soula, C.: L'anémie agastrique expérimentale, Sang **10**:409, 1936.

70. Butt, H. R., and Watkins, C. H.: Occurrence of Macrocytic Anemia in Association with Lesions of the Bowel, Ann. Int. Med. **10**:222, 1936.

71. Hawksley, J. C., and Meulengracht, E.: Intestinal Stricture and Its Association with Pernicious Anaemia, Lancet **2**:124 (July 18) 1936.

72. Konstam, G.: Idiopathic Steatorrhoea with Osteoporosis, Tetany and Megalocytic Anaemia, Proc. Roy. Soc. Med. **29**:631, 1936.

anemia in patients with idiopathic steatorrhea. Battaglia and Arata [73] observed progressive macrocytic anemia in a woman as a result of infestation with Trichocephalus trichiuria. After antiparasitic therapy the blood returned to normal, with no subsequent relapses noted for at least four years after treatment was discontinued.

The production of macrocytic anemia associated with experimental cirrhosis of the liver has been confirmed by Shumacker and Wintrobe.[74] These investigators also noted the presence of hyperplastic bone marrow, which is similar to the bone marrow associated with pernicious anemia during a relapse. There have also been several references [75] to an anemia in which there are a high color index and macrocytosis occurring in association with diseases of the liver. Box and Gill [76] cited a case of syphilitic hepatitis in which there was a response to antisyphilitic treatment only. Hatfield [77] reported a case of splenomegaly and anemia which were cured with oral and parenteral liver therapy. Israëls and Wilkinson [78] described a syndrome characterized by macrocytic anemia, the presence of "free" hydrochloric acid in the gastric contents, hyperplastic bone marrow and failure to respond to the usual types of medication for this type of anemia. The disease has a chronic course with ultimate death. The authors substantiated their findings by citing 4 cases which fulfil the aforementioned requirements.

There appears to be sufficient evidence that the intrinsic factor may be present in the stomach, but owing to hepatic damage the hematopoietic substance cannot be stored and released to the body for utilization, and as a result macrocytic anemia develops. The treatment of the anemia associated with these various conditions depends on which factor or factors are contributing to the cause in each instance. If the intrinsic factor is absent, liver administered orally may be effective; however,

73. Battaglia, A., and Arata, E. C.: Anemia perniciosa por tricocéfalos trichiurus, Prensa méd. argent. **23**:1094 (April 29) 1936.

74. Shumacker, H. B., Jr., and Wintrobe, M. M.: Morphologic Changes in the Blood Associated with Experimentally Produced Hepatic Damage, Bull. Johns Hopkins Hosp. **58**:343, 1936.

75. Wintrobe, M. M.: Relation of Disease of the Liver to Anemia: Type of Anemia, Response to Treatment, and Relation of Type of Anemia to Histopathologic Changes in Liver, Spleen and Bone Marrow, Arch. Int. Med. **57**:289 (Feb.) 1936. Rosenberg, D. H.: Macrocytic Anemia in Liver Disease, Particularly Cirrhosis: Observations on Incidence, Course and Reticulocytosis, with Correlated Study of Gastric Acidity, Am. J. M. Sc. **192**:86, 1936.

76. Box, C. R., and Gill, A. M.: Severe Syphilitic Anaemia of the Pernicious Type, Lancet **1**:24 (Jan. 4) 1936.

77. Hatfield, M. J.: An Unusual Case of Secondary Anemia Simulating Primary Anemia, Kentucky M. J. **34**:76, 1936.

78. Israëls, M. C., and Wilkinson, J. F.: Achrestic Anaemia, Quart. J. Med. **5**:69, 1936.

if there is a disturbance of absorption or storage parenteral therapy should be instituted.

The association of macrocytic anemia with nutritional defects incident to a variety of clinical conditions is reported by Bethell and Rottschaefer.[79] Such conditions are generally characterized by a lowering of the albumin content of the serum, and the anemia may not result from a specific maturation defect. They concluded that determination of serum proteins in conjunction with quantitative studies of the red blood cells often discloses the nature of macrocytic anemia and is of value in the selection of treatment.

ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

HEMOLYTIC ANEMIA

The use of the term spherocytic icterus for the type of hemolytic jaundice marked by the presence of spheroid red blood cells and icterus has been suggested by Krumbhaar.[80] The term is useful as well as descriptive.

After splenectomy the hyperactivity of erythrogenesis in the bone marrow is decreased. Tötterman [81] counted the relative number of developing red blood cells in the material obtained by sternal puncture and found 1,893 nucleated red blood cells for each 400 white blood cells before splenectomy, but seven months after the removal of the spleen the number fell to 110. Löwinger [82] studied the marrow of 6 patients with the disease and found that the proportion of immature red blood cells was greatly increased. In none of his studies did he observe any megaloblasts in the marrow of these patients.

The intensive stimulus to blood regeneration in hemolytic jaundice may lead to extramedullary myelopoiesis. Gleave [83] described the formation of large masses of bone marrow along dorsal vertebral bodies in a 28 year old man who died after the operative removal of a 43 ounce (1.3 Kg.) spleen. The masses, eight in all, lay behind the pleura and arose in the angle between the vertebral bodies and the ribs. The blood

79. Bethell, F. H., and Rottschaefer, G.: Interpretation of Macrocytosis with Especial Reference to Developmental Abnormalities of Red Blood Cell and to Hypoproteinemia: Preliminary Report, Univ. Hosp. Bull., Ann Arbor **2**:65, 1936.

80. Krumbhaar, E. B.: Hemolytic Jaundice—Spherocytic Icterus, J. A. M. A. **107**:1739 (Nov. 21) 1936.

81. Tötterman, G.: Bone Marrow in Hemolytic Jaundice and Contribution to Question of Nature of Megaloblasts, Finska läk.-sällsk. handl. **79**:686, 1936.

82. Löwinger, S.: Das Bild des Knochenmarkes bei der konstitutionellen hämolytischen Anämie (Ikterus Haemolyticus), Folia haemat. **54**:27, 1935.

83. Gleave, H. H.: Paravertebral Heterotopia of Bone Marrow in a Case of Acholuric Jaundice, J. Path. & Bact. **42**:538, 1936.

supply was the same as that of the vertebral bodies, suggesting a direct extension of the marrow as a result of the intensive erythroblastic activity.

Thompson [84] summarized the experience of the splenic disease clinic of the Presbyterian Hospital of New York with 45 patients. The symptoms of typical hemolytic jaundice were promptly, completely and permanently relieved by splenectomy, while those of the atypical forms were not. The hemolytic tendency in patients with spherocytosis may remain latent, first appearing at intervals from the age of 6 weeks to 58 years. When the disease was once active, spontaneous remission did not occur. The inverse relation was pointed out in man and animals between the mean diameter of the red blood cells and the strength of the solution of sodium chloride in which hemolysis begins.

ANEMIA ASSOCIATED WITH CANCER

The blood picture associated with cancer is not pathognomonic, nor does it give any information as to the site of the lesion or the extent of the malignant process. If anemia is present it may be either microcytic or macrocytic, and the color index may be low or high. There is usually leukocytosis. Mogensen [85] studied the blood of 75 patients with cancer of the stomach. Thirty-one per cent of the patients had no anemia. For the entire group the average hemoglobin value was 72.8 per cent. For those with anemia there appeared to be no relationship between the severity of the anemia and the age, sex or duration of the existence of the malignant growth. Thus the presence or absence of anemia was claimed to be of no clinical value in the diagnosis of a malignant process.

On the other hand, the type of anemia present may confuse the clinical picture considerably. Waugh [86] reported 2 cases of carcinoma of the bone marrow with resulting hemolytic anemia. Kiser and Rosenak [87] also noted a hemolytic type of anemia in cases of carcinoma of the stomach with metastasis to the bone marrow. The peripheral blood showed a diminution in the red cell count, with a corresponding decrease in the hemoglobin value. Many immature red and white blood cells were observed in studies of stained blood films. In these cases the fragility of the red blood cells was normal, although in similar instances

84. Thompson, W. P.: Hemolytic Jaundice: Its Diagnosis, Behavior and Treatment; a Review of Forty-Five Cases, J. A. M. A. **107**:1776 (Nov. 28) 1936.

85. Mogensen, E.: Anemia Associated with Cancer of Stomach, Hospitalstid. **79**:85 (Jan. 28) 1936.

86. Waugh, T. R.: Hemolytic Anemia in Carcinomatosis of the Bone Marrow, Am. J. M. Sc. **191**:160, 1936.

87. Kiser, E. F., and Rosenak, B. D.: Myelophthisic Anemia in a Case of Carcinoma of the Stomach, J. A. M. A. **107**:963 (Sept. 19) 1936.

it has been reported as increased. Waugh suggested that the anemia is produced by a toxic substance. Kiser and Rosenak expressed the belief that it may be a compensatory phenomenon or an evidence of irritation of the bone marrow.

The differential diagnosis between pernicious anemia and carcinoma of the stomach is most difficult when the latter is associated with macrocytic anemia. Silverman [88] reported the case of a man who had been successfully treated for pernicious anemia for six years, and in whom carcinoma of the stomach then developed. This was substantiated by autopsy. A similar case was reported by van der Sande.[22] Silverman said he thought that the association of these two diseases may be coincidental, and he suggested that changes in the p_H alter the gastric wall and allow the development of carcinoma. There have been frequent references in the literature suggesting that the macrocytic anemia associated with carcinoma of the stomach is the result of interference in the production of the intrinsic factor in the stomach. Goldhamer [88] recently reported the absence of the intrinsic factor in the gastric contents of a patient who had macrocytic anemia associated with linitis plastica. The anemia was eliminated after the oral administration of desiccated stomach. Hulbert [89] reported a case of adenocarcinoma of the stomach associated with hyperchromic anemia in which there was no response either to liver or to iron.

Sugiura and Benedict [90] studied the effect of an anemia-producing diet on the growth of carcinoma, sarcoma and melanoma in animals. They concluded that the anemia per se did not affect the growth of tumors but that the rate of growth of the malignant process was dependent on the nutritive state of the animals. The rate of growth of tumors in animals on an inadequate diet and in a poor nutritive state was greatly retarded.

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION

The importance of cytoplasmic and nuclear changes which occur in the neutrophils in severe infectious states was emphasized by Mendell, Meranze and Meranze.[91] In their opinion the presence of toxic

88. Goldhamer, S. M.: Linitis Plastica—the Absence of the Intrinsic Factor in the Gastric Contents, read at the meeting of the Michigan Academy of Letters, Science and Arts, March 1937.

89. Hulbert, N. G.: Adenocarcinoma of the Stomach and Hyperchromic Anaemia, Lancet **2**:74 (July 11) 1936.

90. Sugiura, K., and Benedict, S. R.: The Effect of an Anemia-Producing Diet on the Growth of Carcinoma, Sarcoma and Melanoma in Animals, Am. J. Cancer **26**:115, 1936.

91. Mendell, T. H.; Meranze, D. R., and Meranze, T.: Comparative Study of Cytoplasmic and Nuclear Changes in Neutrophils in Severe Infectious States, Am. J. M. Sc. **192**:316, 1936.

granules in the cytoplasm of the neutrophils, the vacuolation of the cytoplasm and the presence of bluish areas in the cytoplasm are a more reliable and accurate guide of the severity and prognosis of an infection than changes noted in the nuclei. The cytoplasmic changes appear to occur earlier in severe infections and last longer than the nuclear changes. As a substitute for the Schilling index the authors suggested the degenerative index—an equation with the number of degenerated neutrophils as the numerator and the total number of neutrophils as the denominator. The severity of the infection is thought to be mild, moderate, severe or grave if the number of neutrophils with cytoplasmic changes is 25, 50 or 75 per cent or more, respectively.

Gibson [92] reported a case of acute hemolytic anemia, similar to Lederer's, in which the disease was due to dental sepsis. Studies of the blood were made by Goodrich and Smith [93] for patients with coronary occlusion. The average white blood cell count was from 13,000 to 18,000 per cubic millimeter. The highest leukocyte counts occurred in the fatal cases. Eosinophils were absent during the active process and present during convalescence. In the opinion of these authors the Schilling count may be used as an index for the prognosis.

In patients with peptic ulcer Ugelli [94] noted lymphocytosis and eosinophilia. He interpreted these findings not as being characteristic of ulcer but as an indication of the vagotonic constitution of the patient. The blood picture was altered by the complication of infection or hemorrhage which caused neutrophilia. These changes disappeared after operation. Tötterman [95] observed the presence of immature myeloid cells and associated leukocytosis in cases of severe polyarthritis and pneumonia.

ANEMIA ASSOCIATED WITH ENDOCRINE DYSFUNCTION

The blood picture associated with thyroid dyscrasias has long been a subject of controversy. Many authors have observed a macrocytic anemia in conjunction with myxedema, while others have reported a microcytic anemia. The anemia may be directly related to the dysfunction of the thyroid gland, or it may exist as an independent condition. Holbøll [96] reviewed a series of 28 cases of myxedema. All the patients

92. Gibson, P. C.: A Case of Acute Febrile Anaemia Due to Dental Sepsis, Lancet **1**:994 (May 2) 1936.

93. Goodrich, B. E., and Smith, F. J.: Nonfilament Leukocyte Count After Coronary Artery Occlusion, Am. Heart J. **11**:581, 1936.

94. Ugelli, L.: Distribuzione dei gruppi sanguigni negli individui portatori di ulcere gastroduodenali, Policlinico (sez. prat.) **43**:1591 (Sept. 7) 1936.

95. Tötterman, G.: So-Called Myeloid Reaction, Finska läk.-sällsk. handl. **79**:880, 1936.

96. Holbøll, S. A.: Anemia in Myxedema Patients, Acta med. Scandinav. **89**:526, 1936.

were women. Their ages ranged from 35 to 64 years. The average duration of their symptoms was six years. Thirteen of the patients had hemoglobin levels below 70 per cent, and in 7 the range was between 70 and 79 per cent. The color index was normal or slightly less than normal in all instances. Eosinophilia was never observed. Lymphocytosis was usually present, the average number of lymphocytes being 50 per cent and the highest value observed 62 per cent. With the administration of thyroid the lymphocytes decreased in number. Holbøll noted also that the anemia associated with myxedema was most satisfactorily influenced by thyroid medication or by a combination of thyroid and iron. This observation was substantiated by the experiments of Bisgard and Sharpe.[97] They thyroidectomized 32 rats, producing myxedema and associated macrocytic anemia. The anemia could not be eliminated with either liver extract or iron but readily responded to thyroid medication.

Zondek and Kaatz[98] noted an increase in the number of platelets in the circulating blood after the use of thyroid preparations. The increase occurred within from twenty-four to forty-eight hours and disappeared in seventy-two hours. The thyrotropic hormone of the pituitary gland was observed to have the same effect, but its action was more protracted. Epinephrine had a variable influence on the platelets. In some instances the number of platelets was increased; in others it was decreased.

HYPOCHROMIC AND MICROCYTIC ANEMIA OF THE IRON DEFICIENCY TYPE

Significant advances in the study of the defective formation of blood associated with a disturbed metabolism of iron have during the past year pursued three lines of inquiry: investigations concerning the absorption, storage and utilization of iron in experimental anemia; observations of the changes in the blood following gastric operations in man and in animals, and consideration of the factors involved in the lowering of blood values during pregnancy. The relationship of anemia to pregnancy will be discussed under a separate heading.

Whipple and Robscheit-Robbins,[99] continuing their work on dogs subjected to prolonged repeated loss of blood, found that iron given

97. Bisgard, J. D., and Sharpe, J. C.: Relation of Thyroid Gland to Hematopoiesis, J. A. M. A. **108**:589 (Feb. 13) 1937.

98. Zondek, H., and Kaatz: Hormonal Regulation of Number of Blood Platelets in Blood, Brit. M. J. **2**:387 (Aug. 22) 1936.

99. Whipple, G. H., and Robscheit-Robbins, F. S.: Iron and Its Utilization in Experimental Anemia, Am. J. M. Sc. **191**:11, 1936.

intravenously to anemic and iron-depleted animals was returned quantitatively as newly formed hemoglobin on the basis of 10 mg. of iron to 3 Gm. of hemoglobin, regardless, within limits of tolerance, of the quantity of iron injected. When iron was given by mouth to these standard anemic dogs the effect on the production of hemoglobin was not proportional to the dose administered, the maximum utilization of iron being 35 per cent of an optimal dose of 40 mg. daily for two weeks. They found that a whole liver supplement to inorganic iron given by mouth produced a summation effect which could not be accounted for solely by the iron content of the liver. However, of especial interest is their observation that no such summation effect followed the feeding of liver concurrently with the intravenous administration of iron. Apparently the stimulus to erythropoiesis occasioned by the presence of relatively large amounts of iron in the circulating blood was maximal and therefore could not be augmented by the usually omnipotent liver. The importance of this conclusion lies in its intimation that liver in the treatment of the anemia of chronic hemorrhage supplies no deficiency but that its effectiveness in supplementing iron depends on promotion of the absorption or utilization of the metal.

Whipple and Robscheit-Robbins found no difference in the effectiveness of iron given by mouth whether in the ferrous, ferric or reduced state. The formation of an Eck fistula or removal of the spleen reduced the utilization of iron given by vein.

Although the work of these investigators on standard anemic dogs advances materially the understanding of the metabolism of iron, the direct application of their findings to clinical practice is hazardous. As they pointed out, the apparently superior results gained from the intravenous over the oral administration of iron in their experiments does not justify the adoption of this route in the treatment of patients. Iron by vein is decidedly toxic, and, moreover, one is not greatly concerned with a maximal percentage of utilization of therapeutic preparations of iron. A daily conversion of 25 or 30 mg. of iron into hemoglobin is optimal, although one may give from five to fifty times this amount.

The uniform effectiveness of iron, regardless of its chemical state, is presumably dependent on reduction to the ferrous form by a normally functioning stomach possessed by dogs made anemic by bleeding but not by those patients who present the more difficult therapeutic problems. Fürth and Scholl[100] determined the absorption of ferrous and ferric compounds from ligated loops of rabbits' intestines. The range of percentage of absorption of the ferrous preparations was from 76 to

100. Fürth, O., and Scholl, R.: Absorption of Ferrous and Ferric Compounds from the Intestines of Rabbits, J. Pharmacol. & Exper. Therap. **58**:14, 1936.

39.7; the absorption of ferric compounds, from 30.5 to 19.8. Absorption of ferrous iron was decidedly impaired by an acid reaction of the intestinal contents.

Iron in the animal economy appears to play three distinct physiologic rôles: That contained in hemoglobin normally constitutes the greatest portion and is concerned with the transference of oxygen; that possessed by the parenchyma cells and by hemoglobin in the muscle is required for local cell metabolism, and that stored in the liver, spleen and elsewhere forms an inactive reserve to be used primarily in the replacement of hemoglobin in the blood stream. Hahn and Whipple [101] found in the case of their standard anemic dogs that there was a rapid turnover of iron in the tissues. After iron supplements were fed for short periods, no storage of the metal was found in the liver; the absorbed iron was formed almost immediately into hemoglobin. Even after longer experiments only small amounts of iron were stored so long as there was a need for hemoglobin. Iron given by vein was stored to a large extent in the liver and spleen. The iron contained within parenchyma cells and hemoglobin of the muscles is not drawn on, no matter how severe the anemia. Moreover, the intravenous administration of iron results in no surplus storage in this tissue.

Schultze, Elvehjem and Hart [102] found that rats made severely anemic by a diet deficient in iron and copper had depleted stores of copper. The feeding of iron and copper for seven days caused only a 5 per cent retention of copper, although maximum hemoglobin formation occurred. Similar experiments on pigs revealed that a deficiency of iron but not of copper could be corrected with iron alone. When both iron and copper were deficient, both were required for cure of the anemia, but there was no apparent storage of the copper in the bone marrow. In a subsequent paper the same authors [103] reported that the copper content of the blood of pigs suffering from nutritional anemia due to iron and copper deficiency falls to extremely low levels. Apparently a minimum copper level of the blood is required for rapid continued erythropoiesis to take place.

Investigation of the changes in the blood produced experimentally by operations on the digestive tract have been carried out by Kellogg,

101. Hahn, P. F., and Whipple, G. H.: Iron Metabolism: Its Absorption, Storage and Utilization in Experimental Anemia, Am. J. M. Sc. **191**:24, 1936.

102. Schultze, M. O.; Elvehjem, C. A., and Hart, E. B.: Studies on the Copper and Iron Content of Tissues and Organs in Nutritional Anemia, J. Biol. Chem. **116**:93, 1936.

103. Schultze, M. O.; Elvehjem, C. A., and Hart, E. B.: Studies on the Copper Content of the Blood in Nutritional Anemia, J. Biol. Chem. **116**:107, 1936.

Mettier and Purviance.[104] Working with dogs, they combined the experimental methods of Whipple, based on repeated bleeding and standard diets, with gastrectomy. They found that after removal of the stomach the capacity to produce hemoglobin on a beef-supplemented diet was greatly reduced. Alt [105] found that resection of 40 per cent of the small intestine of rats produced no anemia. When, however, 80 per cent was removed, anemia, usually hypochromic, developed, which he attributed chiefly to impaired absorption of iron. A further report on the effects of gastrectomy in the rat has been made by Bussabarger and Jung.[65] After removal of the stomach, nutrition was seriously impaired, and severe microcytic hypochromic anemia developed. Iron by mouth or by injection had a beneficial effect on the anemia, whereas liver extract and vitamins, among other substances, were of no value.

One hundred and twenty patients with achylic chloranemia and 200 patients with pernicious anemia were considered by Fleischhacker and Klima [106] with reference to a previous history of gastro-intestinal operations. In 18 of those with achylic chloranemia, anemia developed after operation; all were women. Nine patients, 4 of them men, acquired pernicious anemia after operation. These authors stated the opinion that a mere diminution in the size of the stomach by surgical removal is not a sufficient cause for anemia. One of their patients had polycythemia after almost total resection of the stomach. Frequently secondary changes occur at the site of the operation, and in their opinion these are the principal causes of the anemia.

Approaching the problem from the converse aspect, Lublin [107] studied the blood of 46 patients who returned to the clinic for various complaints other than hemorrhage after either gastro-enterostomy, with or without exclusion of the pylorus, or a Billroth II operation. Sixty-nine per cent of these patients had hypochromic anemia. Lowered blood values were especially prevalent among those who had had a Billroth II operation or an operation for exclusion of the pylorus. Females were predominantly affected. Although achlorhydria or hypochlorhydria was usually present in these cases of anemia, 4 patients secreted a normal amount of hydrochloric acid. Postoperative intestinal disturbances bore no relation to the occurrence of anemia. Lublin claimed that the causes

104. Kellogg, F.; Mettier, S. R., and Purviance, K.: Studies on Hypochromic Anemia in Dogs: Evaluation of Standard Bread Diet and of Meat Diet on Formation of Hemoglobin Before and After Gastrectomy, J. Clin. Investigation **15**:241, 1936.

105. Alt, H. L.: Extensive Resection of Small Intestine in Rat with Special Reference to Anemia, Am. J. Digest. Dis. & Nutrition **3**:169, 1936.

106. Fleischhacker, H., and Klima, R.: Ueber Anämien nach Magen- und Darmoperationen, Ztschr. f. klin. Med. **129**:227, 1935.

107. Lublin, H.: On Anemia Following Gastric Operations, Am. J. Digest. Dis. & Nutrition **3**:8, 1936.

of this type of anemia are to be found chiefly in the stomach, duodenum, liver and perhaps pancreas.

Additional evidence of the rôle of the normally functioning stomach in the absorption of iron is afforded by the work of Kellogg and Mettier.[108] They found that food iron was not utilized for hemoglobin regeneration by patients treated for peptic ulcer with an alkaline regimen. The hemoglobin value increased after discontinuance of the alkali. Their observations are of more theoretical than practical importance, since medicinal iron in suitable doses is effectively utilized in spite of alkali therapy. Schiødt [109] reported the results of treatment in Meulengracht's clinic for patients with peptic ulcer complicated by hemorrhage. Those treated even from the first day of hemorrhage with a general diet consisting of strained food, and ferrous lactate, 0.5 Gm. three times a day, showed a gain in the blood count, especially the color index, and in general well being much more rapidly than those who received a progressive Sippy type of treatment with the same quantity of medicinal iron. He did not mention the use of alkali.

Ahlbom [110] questioned 150 women with squamous cell carcinoma of the mouth, pharynx or esophagus concerning previous signs of simple achlorhydric anemia and the Plummer-Vinson syndrome. Seventy per cent gave affirmative replies. He suggested that these conditions may be precancerous. Rasmussen [111] found a 12 per cent incidence of hypochromic anemia among 460 patients with pulmonary tuberculosis; 60 per cent of these were cured of anemia by iron therapy. There was no evidence that the tuberculous process in itself had a deleterious effect on erythropoiesis. In some instances there appeared to be a relationship between anemia and intestinal tuberculosis.

No recent advances of importance have been made in the treatment of anemia due to iron deficiency. The subject has been considered by Witts,[112] Strauss,[46] Bloedorn [113] and Lucas and Henderson.[114] In

108. Kellogg, F., and Mettier, S. R.: Effect of Alkaline Therapy for Peptic Ulcer on Utilization of Dietary Iron in Regeneration of Hemoglobin, Arch. Int. Med. **58**:278 (Aug.) 1936.

109. Schiødt, E.: Blood Regeneration in Patients with Hematemesis or Melena from Peptic Ulcer, Treated with Usual Ulcer Cure and with Meulengracht Treatment, Am. J. M. Sc. **192**:163, 1936.

110. Ahlbom, H. E.: Simple Achlorhydric Anaemia, Plummer-Vinson Syndrome, and Carcinoma of the Mouth, Pharynx, and Oesophagus in Women: Observations at Radiumhemmet, Stockholm, Brit. M. J. **2**:331 (Aug. 15) 1936.

111. Rasmussen, H.: Anemia in Patients with Pulmonary Tuberculosis, Norsk mag. f. lægevidensk. **97**:1125, 1936.

112. Witts, L. J.: Therapeutic Action of Iron, Lancet **1**:1 (Jan. 4) 1936.

113. Bloedorn, W. A.: Rôle of Iron in Treatment of Anemia, Minnesota Med. **19**:5, 1936.

114. Lucas, G. H. W., and Henderson, V. E.: On Administration of Iron, Canad. M. A. J. **34**:53, 1936.

general, there has been a trend toward the use of the more stable ferrous preparations given in divided doses to supply approximately 160 mg. of metallic iron daily. Patek [115] has presented clinical evidence of the beneficial effect of chlorophyll and its derivatives as supplements to inorganic iron. In his opinion these pigments, preformed, can be used by the body in the production of erythrocytes.

Nutritional anemia in infancy is generally regarded primarily as an iron deficiency state. The clinical studies of Paxton [116] and of Guest and Brown [117] have added further support to this view and have increased the weight of evidence against the therapeutic value of copper. Continuing their work on the iron and copper content of human blood, Sachs, Levine and Fabian [118] found in the blood of 6 new-born infants an average iron content of 51.79 mg. per hundred cubic centimeters and an average hemoglobin value of 15.45 Gm. per hundred cubic centimeters. Seventy-one children, varying in age from 1½ months to 15 years, showed an average of 40.51 mg. of iron and 12.09 Gm. of hemoglobin per hundred cubic centimeters. As in the case of adults, the authors found that copper and iron maintain a reciprocal relationship in the blood of normal children.

Orten, Smith and Mendel [119] found polycythemia and concurrent hemoglobin deficiency in young rats fed a mineral-deficient ration. The changes, they claimed, were due chiefly, if not entirely, to a lack of calcium and iron. They suggested that calcium may favorably affect the economy of iron in metabolism.

A comprehensive review of the subject of anemia in infancy and early childhood has been published by Josephs.[120]

ANEMIA OF PREGNANCY

In the study of anemia associated with pregnancy, increasing recognition has been given to the multiplicity of factors involved in the

115. Patek, A. J., Jr.: Chlorophyll and Regeneration of the Blood: Effect of Administration of Chlorophyll Derivatives to Patients with Chronic Hypochromic Anemia, Arch. Int. Med. **57**:73 (Jan.) 1936.

116. Paxton, W. T. W.: Nutritional Anaemia in Infancy and Childhood, Glasgow M. J. **125**:153, 1936.

117. Guest, G. M., and Brown, E. W.: Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood: Size and Hemoglobin Content of Erythrocytes in Nutritional Anemia, Am. J. Dis. Child. **52**:616 (Sept.) 1936.

118. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood: Normal Children, Arch. Int. Med. **58**:523 (Sept.) 1936.

119. Orten, J. M.; Smith, A. H., and Mendel, L. B.: Relation of Calcium and of Iron to Erythrocyte and Hemoglobin Content of Blood of Rats Consuming Mineral Deficient Ration, J. Nutrition **12**:373, 1936.

120. Josephs, H. W.: Anemia of Infancy and Early Childhood, Medicine **15**:307, 1936.

lowering of the blood values during gestation. Feldman, van Donk, Steenbock and Schneiders [121] determined the hemoglobin value, cell volume and refractive index of the blood of 20 pregnant women and found evidence of hydremia regularly. The maximum changes occurred at about the two hundred and twentieth day of gestation. On the other hand, there were few or no signs of blood dilution among 40 pregnant cows.

Boycott [122] found that of 222 pregnant women attending the University College Hospital, London, 22 per cent had hemoglobin values below 11 Gm. per hundred cubic centimeters. He agreed with earlier investigators that the increased volume of plasma may produce an apparent anemia and that the effects of hydremia may coexist with true hypochromic anemia. The common anemia of pregnancy, he found, responded well to adequate iron therapy. In New Zealand a 14 per cent incidence during pregnancy of hemoglobin values below 10.28 Gm. per hundred cubic centimeters was reported by McGeorge.[123] He considered that lowered gastric acidity is the principal factor in the etiology of hypochromic anemia of pregnant women, dietary iron is important and contributory causes are diets low in protein and green vegetables and the added demand for iron occasioned by the gravid state. Corrigan and Strauss [124] studied 200 women during the last four months of pregnancy. Alternate patients were given 0.5 Gm. of ferrous sulfate daily. The others received placebos. Of the 100 women taking iron, none had a hemoglobin value of less than 10.9 Gm. per hundred cubic centimeters after delivery; of those not receiving iron, 24 had post partum a value of less than 10.9 Gm. They concluded that hypochromic anemia in pregnancy may be largely prevented by the routine administration of iron, especially in the later months of gestation.

Adair, Dieckmann and Grant [125] calculated the effect of hydremia and gave average and minimum normal blood values which may be expected during pregnancy. Their incidence of anemia was 11.6 per cent, predominantly of the hypochromic and microcytic type. Iron therapy was not always effective, and transfusions were frequently found of value. They suggested that a dietary deficiency other than a lack

121. Feldman, H.; van Donk, E. C.; Steenbock, H., and Schneiders, E. F.: Hydremia as Factor in Anemia of Pregnancy, Am. J. Physiol. **115**:69, 1936.

122. Boycott, J. A.: Anaemia in Pregnancy, Lancet **1**:1165 (May 23) 1936.

123. McGeorge, M.: Anaemia in Gynaecological and Obstetric Practice in New Zealand, J. Obst. & Gynaec. Brit. Emp. **42**:1027, 1935.

124. Corrigan, J. C., and Strauss, M. B.: Prevention of Hypochromic Anemia in Pregnancy, J. A. M. A. **106**:1088 (March 28) 1936.

125. Adair, F. L.; Dieckmann, W. J., and Grant, K.: Anemia in Pregnancy, Am. J. Obst. & Gynec. **32**:560, 1936.

of iron may be operative in these cases. Stevenson [126] analyzed 90 cases of anemia of pregnancy and described 60 as cases of hypochromic anemia and 30 as cases of "pernicious anemia of pregnancy." The latter differed from cases of typical pernicious anemia, and she attributed them to dietary defects. It should be noted that the high incidence of this form of anemia indicates that it was not the type commonly designated as pernicious anemia of pregnancy.

Studies of the blood of 66 pregnant women have been reported by Bethell.[127] Although apparently healthy, 70 per cent of the subjects had blood values too low to be accounted for reasonably by the increased volume of plasma alone. Twenty-eight patients had hypochromic and microcytic anemia. By calculating the amount of iron required by the fetus and subtracting that saved by the absence of menstruation, it was shown that the net loss of iron suffered by the pregnant woman was no greater than that occasioned by serving as donor for a moderate-sized blood transfusion. Data were presented which demonstrated no correlation between the capacity of the stomach to secrete hydrochloric acid and the level of the blood count, thus suggesting that the temporary reduction of the gastric acidity was not a direct cause of lowered blood values in pregnancy. The development of hypochromic anemia during pregnancy was attributed to preexisting iron depletion, and it was suggested that a lack of iron may be recognized before the development of actual anemia by the presence of a lowered color index or of red blood cells of less than normal size. In such cases the administration of iron was recommended. A contrasting type of anemia occurred in 18 of the subjects, characterized by a normal color index and by erythrocytes of normal or increased size. The albumin content of the serum of these patients was abnormally low, and it was suggested that the anemia was caused by an inadequate intake of protein of high biologic value. Supplementing the dietary protein led to correction of the anemia.

Further emphasis of the relative unimportance of pregnancy as a cause of iron deficiency, except in cases of gross postpartum hemorrhage, has been provided by the work of Fullerton.[128] He found hypochromic anemia prevalent among a group of 1,534 women of the poorer classes of Aberdeen, Scotland. The incidence and severity of the anemia increased with the age of the subjects until the menopause but bore no relation to the number of pregnancies. He attributed the anemia to

126. Stevenson, M.: Investigation of Anaemias of Pregnancy and Puerperium, J. State Med. **44**:467, 1936.

127. Bethell, F. H.: Blood Changes in Normal Pregnancy and Their Relation to Iron and Protein Supplied by Diet, J. A. M. A. **107**:564 (Aug. 22) 1936.

128. Fullerton, H. W.: Anaemia in Poor Class Women, with Special Reference to Pregnancy and Menstruation, Brit. M. J. **2**:523 (Sept. 12) 1936; Hypochromic Anaemias of Pregnancy and Puerperium, ibid. **2**:577 (Sept. 19) 1936.

a diet low in iron, averaging for this group a daily intake of 7.71 mg. of the metal, and to the loss of iron throughout reproductive life. He concluded:

> Menstruation constitutes an iron loss at least as great as that due to pregnancy and lactation . . . even in women of the poorer classes the transference of iron from the mother to the uterus and its contents is compensated wholly or to a large extent by dietary iron. In cases where this demand exceeds the retention of dietary iron the degree of maternal iron deficiency which results is only slight. Where hypochromic anemia in pregnancy is marked, anemia has probably existed before the pregnancy, but has been made more apparent by physiological hydremia. . . .

The incidence of symptoms of toxemia of pregnancy was related to the presence of hypochromic anemia in a series of cases reported by Moore and Williams.[129] Only 1 of 35 patients treated with iron showed symptoms of toxemia, whereas symptoms of a mild to a moderate degree of toxemia were noted in 6 of 34 untreated patients. However, it has been the experience of most observers that no obvious relationship exists between the common forms of anemia in pregnancy and the occurrence of toxemia. It seems more probable that the rarer grave anemias of pregnancy may have their origin in toxemia.

Daniachi [130] reported 6 cases of severe anemia not characterized by hypochromia. The bone marrow in these cases revealed either megaloblastic or normoblastic hyperplasia. The author claimed that, aside from pernicious anemia of pregnancy, these anemias are of widely different types. They are all closely associated with toxemia, and their outcome depends on the result of the underlying toxic condition. Adequate prepartal care, he maintained, is the best prophylaxis of these severe anemias.

Heilbrun [131] reported a case of pernicious anemia of pregnancy in which studies of the bone marrow revealed megaloblastic hyperplasia. After remission had been induced by the parenteral administration of liver extract, the marrow picture returned to normal.

DEFINITE DISEASE ENTITIES OF THE BLOOD

POLYCYTHEMIA

A patient who showed well marked symptoms of polycythemia for fifteen years is reported on by Welbourn.[132] There were no marked

129. Moore, J., and Williams, E. M. P.: Anaemia and Toxaemia of Pregnancy, Brit. M. J. **2**:528 (Sept. 12) 1936.

130. Daniachi, M. A.: Blutbildung und klinischer Verlauf der Graviditätsanämien, Monatschr. f. Geburtsh. u. Gynäk. **100**:328, 1935.

131. Heilbrun, N.: State of Sternal Bone Marrow in Case of Macrocytic (Pernicious) Anemia of Pregnancy, J. A. M. A. **107**:27 (July 4) 1936.

132. Welbourn, M. A.: Polycythemia Vera: Report of an Unusual Case, in Medical Papers Dedicated to H. A. Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc., 1936, p. 632.

remissions, either spontaneous or induced, and no significant changes in the vascular system were noted.

Dustin [133] has added another case of polycythemia in which anemia developed to those previously described by others. The red blood cell count was 6,840,000 per cubic millimeter originally. No splenic enlargement was noted. During the course of two years a red blood cell count of 2,300,000 per cubic millimeter was reached, with a color index of 0.56. Improvement followed the use of iron therapy. (Intestinal hemorrhage was probably an important etiologic factor.) In a 20 year old woman with pulmonary arteriolar sclerosis, dilatation of the pulmonary artery and hypertrophy of the right ventricle, Darley and Doan [134] found a red blood cell count of 7,480,000 per cubic millimeter. A curious feature was the abnormally high intake of salt (as much as 3 pounds [1.3 Kg.] in one week) to which the patient was accustomed.

Additional cases of polycythemia and duodenal ulcer are described by Kraemer and Asher.[135] Biweekly gastric lavage with solution of sodium bicarbonate for three months did not influence the height of the red blood cell count (8,750,000 to 9,500,000 per cubic millimeter).

Herzog [136] fed his polycythemic patients on diets containing only 0.7 Gm. of animal protein per day. He obtained improvement in the symptoms within one week and reduction in the number of red blood cells to normal in from two to nine weeks. The cases included both the Geisbock and the Vaquez type of polycythemia. After one or two months the intake of milk, fish and cheese was increased without harm.

Two women with an expanding intracranial lesion and polycythemia were reported on by Barker and Craig.[137] The volume of blood was normal, and splenomegaly was absent. The red blood cell counts were 9,160,000 and 6,560,000 per cubic millimeter, respectively.

Emile Weil [138] studied a patient aged 56 years with a red blood cell count of 8,070,000 per cubic millimeter and with an enlarged spleen.

133. Dustin, P., Jr.: A propos d'un cas d'anémie apparue chez un ancien hyperglobulique, Sang **10**:517, 1936

134. Darley, W., and Doan, C. A.: Primary Pulmonary Arteriosclerosis with Polycythemia, Associated with the Chronic Ingestion of Abnormally Large Quantities of Sodium Chlorid (Halophagia), Am. J. M. Sc. **191**:633, 1936.

135. Kraemer, M., and Asher, M.: Association of Erythremia and Duodenal Ulcer, Am. J. M. Sc. **191**:234, 1936.

136. Herzog, F.: Die Behandlung der Polyzythämie mit an tierischem Eiweiss sehr armer Diät, Deutsche med. Wchnschr. **62**:960 (June 12) 1936.

137. Barker, N. W., and Craig, W. M.: Relative Polycythemia Associated with Hypophyseal and Diencephalic Lesions, Proc. Staff Meet., Mayo Clin. **11**: 548 (Aug. 26) 1936.

138. Weil, P. E.: Un cas de splénomégalie avec polyglobulie terminée en syndrome d'anémie type von Jaksch-Luzet, Sang **10**:752, 1936.

Large doses of x-rays over the spleen did not reduce the red blood cell count. No improvement followed liver or spleen therapy. The red blood cell count was reduced to normal with phenylhydrazine, and later the spleen was removed. Polycythemia returned. Roentgen therapy was given over the bones. Severe anemia with a leukemic blood picture followed (nucleated cells, 103,400 per cubic millimeter). The history in this case illustrates the interrelationships of polycythemia, leukemia and forms of anemia.

Liver extract, and to a less extent desiccated hog stomach, produced a temporary fall in the number of red blood cells in rats which had been made polycythemic by the administration of a milk diet supplemented by salts of cobalt, iron, copper and manganese (Marshall[139]). The decrease (13 per cent) was maintained only until the administration of liver extract was stopped, after which the polycythemia returned. Fresh whole liver caused a temporary increase in the erythrocyte count, but fresh lean meat produced no change. Marshall concluded that the liver produces a hormone which exercises an inhibiting action on hematopoiesis.

That the gastric juice in polycythemia is rich in the "intrinsic factor of Castle" was concluded by Barath and Fülöp,[140] after inducing remissions in pernicious anemia by the rectal administration of a beef digest from the stomachs of polycythemic patients. The loss of gastric juice had a favorable but temporary effect on the polycythemic patients.

In fish, frogs, dogs and men asphyxia is followed by a slight increase in the red blood cell count (Binet and Strumza[141]).

In 9 cases of polycythaemia vera Bowie[142] found an average value for serum calcium of 11.3 mg. per hundred cubic centimeters. The values were reduced after treatment with phenylhydrazine hydrochloride. The total values for plasma proteins were within normal limits (average, 6.68 Gm. per hundred cubic centimeters). The average specific gravity of the serum was 1.025, but that of the whole blood was elevated to an average of 1.068.

The erythrocyte and leukocyte counts for rats made polycythemic with cobalt are decreased by roentgen therapy, just as in the case of

139. Marshall, L. H.: Antianemic Treatment in Experimental Polycythemia, Am. J. Physiol. **114**:194, 1935.

140. Barath, E., and Fülöp, J.: Untersuchungen über den pathogenetischen Zusammenhang von perniziöser Anämie und splenomegaler Polycythämie, Ztschr. f. klin. Med. **129**:172, 1935.

141. Binet, L., and Strumza, M. V.: La polyglobulie asphyxique, son degré, sa généralité, Sang **9**:927, 1935.

142. Bowie, M. A.: Polycythemia Vera: A Study of the Relationship Between Serum Calcium and Total Proteins of the Serum, in Medical Papers Dedicated to H. A. Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc., 1936, p. 626.

normal rats. De Savitsch and his co-workers [143] found that cobalt did not enhance the regeneration of hematopoietic bone marrow after irradiation but that shielded parts of the bones after irradiation showed compensatory hyperplasia greater than that in the controls.

Irradiation of the body as a whole—"spray therapy"—was used by Hunter [144] in 2 cases of polycythaemia vera and 1 case of Cooley's erythroblastic anemia. About 1,000 roentgens was given over several weeks. Remissions lasting three years were noted.

PURPURA HAEMORRHAGICA

The etiology of purpura is manifold, and as a result various types have been described. The clinical value of the innumerable complex classifications is doubtful. There are three factors which determine the degree of bleeding: (*a*) the platelets, (*b*) the permeability of the capillaries and (*c*) the plasma. The reduction of the number of platelets is ascribed to a dysfunction of the bone marrow with decreased formation of platelets or to an increased destruction by the reticulo-endothelial system (primarily the spleen).

Purpura may be congenital or acquired. Sanford, Leslie and Crane [145] described the case of an infant born with purpura. Both the mother and the grandmother had a similar condition. Three patients with purpura produced by Bacillus pertussis vaccine were observed by Kugelmass.[146] Toxic purpura complicating scarlet fever was noted by Morrish.[147] In some instances purpura may be produced by drugs. Falconer, Epstein and Wever [148] described two types of purpura following the use of arsenicals. In some instances the number of platelets is reduced, while in others there is damage to the capillaries. Thrombopenia following the use of sedormid (allylisopropylacetylcarbamide)

143. de Savitsch, E.; Radford, M.; Blocksom, B. H.; Perry, S. P., and Tupikova, N.: The Effect of Roentgen Irradiation on Experimentally Produced Polycythemia in Rats with Special Reference to Blood and Bone Marrow, Am. J. Roentgenol. **35**:786, 1936.

144. Hunter, F. T.: "Spray X-Ray Therapy" in Polycythemia Vera and in Erythroblastic Anemia, New England J. Med. **214**:1123 (June 4) 1936.

145. Sanford, H. N.; Leslie, E. I., and Crane, M. M.: Congenital Thrombocytopenia, Am. J. Dis. Child. **51**:1114 (May) 1936.

146. Kugelmass, I. N.: Thrombocytopenic Purpura Induced by Pertussis Toxin in Allergic Children, J. A. M. A. **107**:2120 (Dec. 26) 1936.

147. Morrish, J. E.: Toxic Purpura Haemorrhagica Complicating Scarlet Fever, Lancet **1**:949 (April 25) 1936.

148. Falconer, E. H.; Epstein, N. N., and Wever, G. K.: Purpura Haemorrhagica Following the Administration of Neoarsphenamine: The Reaction to Neoarsphenamine Compared with the Reaction to Mapharsen, Arch. Int. Med. **58**:495 (Sept.) 1936.

and phenobarbital has been described by Boas and Erf.[149] Often the etiology of purpura is not known. Finochietto and his colleagues[150] reported the association of exophthalmic goiter and purpura. They were unable to explain the etiology of purpura, although in their opinion the thyroid dysfunction was not the causative factor. Guggisberg[151] described abnormal generalized bleeding complicated by pregnancy. In his opinion pregnancy may improve or exacerbate the existing purpuric condition.

The symptoms associated with purpura are varied, depending on the location and severity of the hemorrhages, the etiology of the condition and any existing diseases which may be present. A case of intussusception following intra-abdominal hemorrhage was observed by Gray.[152]

In an effort to determine the etiology of thrombocytopenic purpura, Tocantins[153] experimentally produced the condition in dogs and observed the cytologic and physical changes in the blood. The animals were given injections of a prepared antiplatelet serum by various routes—intravenous, intraperitoneal and subcutaneous. With the first method the changes occurred most rapidly. Thrombopenia developed within a few minutes and lasted for from forty-eight to seventy-two hours. In from three to five days the number of platelets returned to normal, and it then exceeded the normal level for approximately fourteen days. A peak was noted between the eighth and the twelfth day. Macroplatelets appeared in three or four hours. They varied greatly in shape, size and consistency. Hemolysis occurred during the acute stage. At first leukopenia existed, with a reduction in the number of lymphocytes, monocytes and eosinophils. This was followed by leukocytosis in which the polymorphonuclear cells were greatly increased in number. The bleeding time was markedly prolonged. Tocantins concluded that there was a high correlation between the number of platelets and the degree of clot retraction and also a similar relationship between the clot retraction and the mean bleeding time. In his opinion the permeability of the vessels, capillary and venous pressure, osmotic pressure, viscosity of the

149. Boas, E. P., and Erf, L. A.: Thrombocytopenic Purpura Following Medication with Sedormid and with Phenobarbital, New York State J. Med. **36**:491 (April 1) 1936.

150. Finochietto, R.; del Castillo, E. B., and Parodi, A. S.: Bocio exoftálmico y púrpura hemorrágica trombocitopénica, Semana méd. **2**:1059 (Oct. 15) 1936.

151. Guggisberg, H.: Die gynäkologische und geburtshilfliche Bedeutung der essentiellen thrombopenischen Purpura, Helvet. med. acta **3**:375, 1936.

152. Gray, T.: Henoch's Purpura Causing Acute Obstruction Twice in Eight Days, Lancet **1**:841 (April 11) 1936.

153. Tocantins, L. M.: Experimental Thrombopenic Purpura in the Dog, Arch. Path. **21**:69 (Jan.) 1936; Experimental Thrombopenic Purpura: Cytological and Physical Changes in the Blood, Ann. Int. Med. **9**:838, 1936.

blood and tension of the tissues were important factors in the determination of the bleeding.

Since the etiology of purpura cannot always be determined, treatment frequently results in failure. Many investigators[154] have reported spectacular improvement after splenectomy. Hedenius and Wilander[155] suggested the use of small repeated amounts of heparin to prevent the postoperative formation of thrombi. Klima[156] observed satisfactory results with kephrine hydrochloride when administered orally or intramuscularly. Riolo[157] recommended increasing daily intravenous doses of epinephrine. He stated that the drug regulates the functions of the spleen—more platelets are expelled, the lytic action is decreased, the tone of the capillaries is increased and the bone marrow is stimulated to produce more thrombocytes. Phenylhydrazine was employed by Wallgren.[158] Although the platelets were increased in number with this drug, there was an accompanying hemolysis. He concluded, therefore, that this type of therapy should not be employed. Clerc and his associates[159] injected intravenously pure octylic alcohol in small amounts into 10 patients with purpura. Although the coagulation time was shortened, there was little if any effect on the bleeding time. The mode of action was obscure. Lowenburg and Ginsburg[160] noted the return to normal of all blood values after induced hypercalcemia. They advised the use of calcium gluconate to prevent the development of the toxic symptoms which are produced by parathyroid extract.

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154. Brown, D. N., and Elliott, R. H. E.: The Results of Splenectomy in Thrombocytopenic Purpura: Comparative Study of Ten Cases in Which Splenectomy Was Performed and Eleven Cases Treated by Conservative Methods, J. A. M. A. **107**:1781 (Nov. 28) 1936. Smith, G.: Splenectomy for Thrombocytopenic Purpura, Brit. M. J. **1**:157 (Jan. 25) 1936. Wollstein, M., and Kreidel, K. V.: Blood Picture After Splenectomy in Children, with Special Reference to Platelets, Am. J. Dis. Child. **51**:765 (April) 1936. Curtis, G. M.; Doan, C. A., and Wiseman, B. K.: Splenectomy for Hemoclastic Crises, Ann. Surg. **104**:892, 1936.

155. Hedenius, P., and Wilander, O.: Influence of Intravenous Injections of Heparin in Man on Time of Coagulation, Acta med. Scandinav. **88**:443, 1936.

156. Klima, R.: Ueber ein neues Behandlungsverfahren bei thrombopenischer Purpura, Klin. Wchnschr. **15**:935 (June 27) 1936.

157. Riolo, P.: Terapia splenocontrattile endovenosa di porpore emorragiche, Riforma med. **52**:603 (May 2) 1936.

158. Wallgren, A.: Essais de traitement du purpura thrombopénique par la phénylhydrazine, Rev. franç. de pédiat. **12**:370, 1936.

159. Clerc, A.; Sterne, J.; Delamare, J., and Paris, R.: Sur les effets coagulants et hémostatiques de l'alcool octylique primaire au cours des syndromes hémorragiques, Presse méd. **44**:1681 (Oct. 28) 1936.

160. Lowenburg, H., and Ginsburg, T. M.: Induced Hypercalcemia: Its Possible Therapeutic Relation to Thrombocytopenic Purpura, J. A. M. A. **106**: 1779 (May 23) 1936.

Roentgen therapy has been recommended by Mettier and Stone [161] and Rudisill.[162] Although they have noted improvement in many cases, they also have had many failures. Lorenz [163] has employed vitamin A to regulate splenic function. This substance was given to 20 children for two or three weeks. In some the platelets increased in number; in others there was a decrease. Similar results were observed in experiments on guinea-pigs. Lorenz expressed the belief that the increase in the thrombocyte count is due to stimulation and the decrease to the effect on the regulating system of the spleen. The reports concerning the value of vitamin C in thrombocytopenic purpura are variable. Cotti [164] observed both an increase and a decrease in the coagulation time in different patients. Engelkes [165] and Eufinger and Gaehtgens [166] noted beneficial effects on the capillaries only but no changes in the number of platelets. Wright and Lilienfeld [167] reported failures with the use of cevitamic acid for purpura.

A prognostic venom test reaction for purpura has been devised by Peck, Rosenthal and Erf.[168] One-tenth cubic centimeter of 1:3,000 dilution of standardized moccasin venom is injected intracutaneously. Saline solution is used as a control. The presence of purpuric spots within one hour at the site of the injection of the snake venom, with no reaction in the control, is interpreted as a positive result of the test. A delayed reaction may be noted within twelve hours when there is a diffusion of blood at the site of injection. Tests are carried out before and during treatment. When the test shows a negative result, improvement has been obtained. The test is used to determine whether or not splenectomy is indicated. One objection to this procedure is that in

161. Mettier, S. R., and Stone, R. S.: The Effect of Roentgen Ray Irradiation on Platelet Production in Patients with Essential Thrombocytopenic Purpura Haemorrhagica, Am. J. M. Sc. **191**:794, 1936.

162. Rudisill, H., Jr.: The Successful Treatment of Essential Thrombopenia with Hemorrhage by Roentgen Rays, J. A. M. A. **107**:2119 (Dec. 26) 1936.

163. Lorenz, E.: Influence of Vitamin A on Thrombocytes, Ztschr. f. Kinderh. **58**:515, 1936.

164. Cotti, L.: Ulteriori ricerche "in vivo" sull'influenza della vitamina C sulla coagulazione del sangue, Haematologica **17**:483, 1936.

165. Engelkes, H.: Treatment of Haemorrhagic Disorders with Vitamin C, Lancet **2**:1285 (Dec. 7) 1935.

166. Eufinger, H., and Gaehtgens, G.: Ueber die Einwirkung des Vitamin C auf das pathologisch veränderte weisse Blutbild, Klin. Wchnschr. **15**:150 (Feb. 1) 1936.

167. Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Special Reference to Its Effects on Capillary Fragility, Arch. Int. Med. **57**:241 (Feb.) 1936.

168. Peck, S. M.; Rosenthal, N., and Erf, L. A.: The Value of the Prognostic Venom Reaction in Thrombocytopenic Purpura, J. A. M. A. **106**:1783 (May 23) 1936.

an active state the injection of saline solution may cause damage to the capillaries, with resulting bleeding.

The aforementioned authors recommended also the use of snake venom for treatment. The material is injected subcutaneously. Cambrook [169] stated that hot snake venom when applied locally is of great value in dental surgery to control bleeding. The value of the various types of therapy for purpura has been summarized by Tidy.[170] Since spontaneous cure is not uncommon, a conservative attitude must be adopted concerning the value of the various therapeutic agents recommended.

HEMOPHILIA

The clinical features by which the diagnosis of hemophilia may be established have been summarized by Eley.[171] The essential findings are its inheritance, the occurrence in males, a history of repeated hemorrhages, a prolonged clotting time and a normal bleeding time. The disease is apparently transmitted according to the mendelian laws by the female. Eley cited a case in which the malady appeared in a woman whose parents were members of families in which there was hemophilia.

There is considerable diversity of opinion regarding the nature of the blood elements concerned with the clotting mechanism. Some investigators believe there is a slow disintegration of the blood platelets owing to a low thrombin and a high antithrombin content of the blood. Recently it was demonstrated by Eagle [172] that there is a delay in the formation of thrombin.

The complications of hemophilia are usually the result of abnormal bleeding into the various organs and tissues of the body. Hill and Brooks [173] reported a case of Volkmann's ischemic contracture and gangrene of the fingers. Thomas [174] reviewed a series of 98 cases of hemophilia and pointed out that 78.5 per cent of the patients had some orthopedic involvement. Approximately 60 per cent of the patients had permanent deformities due to hemorrhages. The occurrence of hemo-

169. Cambrook, J. D.: Snake Venom and Its Use in Dental Haemorrhage, Proc. Roy. Soc. Med. **29**:281, 1936.

170. Tidy, H. L.: Treatment of Haemorrhagic Diseases, Brit. M. J. **1**:850 (April 25) 1936.

171. Eley, R. C.: Hemophilia, Internat. Clin. **2**:202, 1936.

172. Eagle, H.: Studies on Blood Coagulation: The Rôle of Prothrombin and of Platelets in the Formation of Thrombin, J. Gen. Physiol. **18**:531, 1935; Studies on Blood Coagulation: The Formation of Fibrin from Thrombin and Fibrinogen, ibid. **18**:547, 1935; Studies on Blood Coagulation: The Nature of the Clotting Deficiency in Hemophilia, ibid. **18**:813, 1935.

173. Hill, R. L., and Brooks, B.: Volkmann's Ischemic Contracture in Hemophilia, Ann. Surg. **103**:444, 1936.

174. Thomas, H. B.: Some Orthopaedic Findings in Ninety-Eight Cases of Hemophilia, J. Bone & Joint Surg. **18**:140, 1936.

philic pseudotumors involving the smaller bones and joints has been described by Firor and Woodhall.[175] Priest[176] cited a case in which there was epidural hemorrhage in association with hemophilia and commented on the fact that neurologic complications are rare.

At present no known specific therapy has been devised. Some of the common agents employed are whole blood, citrated blood, human plasma, human and animal serum, defibrinated blood, hemostatic preparations, fibrinogen and cephalin in suspension, calcium chloride, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts and a special dietary regimen. Recently, Timperley and his associates[177] reported excellent results in the control of hemorrhage with parenteral injections of an alcohol-acetone extract of egg white. Tocantins[178] noted similar results with the administration of antiplatelet serum.

BANTI'S DISEASE

Banti's disease was first described as a clinical entity in 1881 by the author whose name it bears. The etiology was ascribed to an unidentified toxic substance which primarily affected the spleen and secondarily involved the liver. The pathologic changes noted were sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver. The cure was splenectomy.

The existence of the disease is questioned by many investigators, and some authors[179] have stated that as a clinical entity it does not exist. The pathologic changes which were thought by Banti to be specific have been produced experimentally in animals by obstruction of the splenic and portal veins and have been demonstrated at autopsy to be secondary to hepatic disorders or, as Rø[179b] showed, the result of the formation of thrombi in the portal system.

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175. Firor, W. M., and Woodhall, B.: Hemophilic Pseudotumor: Diagnosis, Pathology and Surgical Treatment of Hemophilic Lesions in Smaller Bones and Joints, Bull. Johns Hopkins Hosp. **59**:237, 1936.

176. Priest, W. M.: Epidural Haemorrhage Due to Haemophilia Causing Compression of Spinal Cord, Lancet **2**:1289 (Dec. 7) 1935.

177. Timperley, W. A.; Naish, A. E., and Clark, G. A.: A New Method of Treatment in Haemophilia, Lancet **2**:1142 (Nov. 14) 1936.

178. Tocantins, L. M.: Effets de l'injection du sérum antiplaquettes à trois sujets hémophiles et à un sujet normal. Action de divers sérums sur le sang "in vitro," Sang **10**:582, 1936.

179. (*a*) Banti's Disease, Cabot Case 21341, New England J. Med. **213**:373 (Aug. 22) 1935. (*b*) Rø, J.: Stricture of Splenic Vein; Splenic Pylephlebostenosis, Norsk mag. f. lægevidensk. **97**:603, 1936. (*c*) Rousselot, L. M.: Rôle of Congestion (Portal Hypertension) in So-Called Banti's Syndrome: Clinical and Pathologic Study of Thirty-One Cases with Late Results Following Splenectomy, J. A. M. A. **107**:1788 (Nov. 28) 1936.

Rousselot [179c] reviewed 31 cases of so-called Banti's disease, in each of which splenectomy was performed. He reemphasized the fact that enlargement of the spleen was the most common finding, as it was present in every instance. Other common symptoms were weakness, pain, hemorrhage, tiredness and gastro-intestinal complaints. The pathologic changes observed were the same as those which others have described and in no way differed from those seen in chronic congestion of the spleen regardless of the etiology.

The anemia present may be macrocytic or microcytic. Unquestionably microcytic anemia is due to chronic hemorrhage. Macrocytic anemia is probably the result of interference with hematopoiesis due to the failure of the liver to store or present for utilization to the bone marrow the substance necessary for the maturation of the red blood cells. Archi [180] stated that the increase in the diameter of the red blood cells is not associated with all hepatic disorders but occurs only with those in which there is diffuse involvement of the entire parenchyma of the liver. In his opinion the blood picture is of no prognostic significance or diagnostic value.

For several years the accepted treatment for Banti's disease has been splenectomy. A résumé of the early reports is confusing, as in many of the cases reported the condition does not fit into this syndrome. Furthermore, the disease may run a course lasting several years, so that any conclusions concerning the benefits derived from this procedure must be guarded. Rø expressed the opinion that splenectomy is of value. Others (Martin [181] and Moore [182]) have also supported this view, despite the fact that their results have not always been satisfactory or convincing. Because of the high mortality rate associated with splenectomy and the equally good results obtained with conservative measures, Goldhamer [183] suggested that the latter type of therapy is preferable.

HODGKIN'S DISEASE, LYMPHOGRANULOMA AND RELATED CONDITIONS

Lesions of the bones may be demonstrated roentgenographically in from 10 to 15 per cent of patients with Hodgkin's disease. In 3 patients Spencer and Dresser [184] noted a single osseous lesion, which gave rise to the predominating symptoms and simulated a primary bone tumor.

180. Archi, A.: Etudes actuelles sur l'anisocytose des érythrocytes et leurs applications au diagnostic des maladies du foie, Paris méd. **1**:561 (June 13) 1936.

181. Martin, L. C.: Banti's Syndrome in Childhood: Report of Four Cases, Arch. Dis. Childhood. **11**:233, 1936.

182. Moore, S. W.: Portal Thrombosis Following Splenectomy for Splenic Anemia, Surg., Gynec. & Obst. **63**:382, 1936.

183. Goldhamer, S. M.: Splenectomy in Hematopoietic Disorders: Preliminary Report, Univ. Hosp. Bull., Ann Arbor **2**:20, 1936.

184. Spencer, J., and Dresser, R.: Lymphoblastoma (Hodgkin's and Sarcoma Type) of Bone, with Report of Three Cases Simulating Primary Malignant Tumor of Bone, New England J. Med. **214**:877 (April 30) 1936.

These authors [185] noted 120 lesions of bones in 66 cases, as follows: lumbar region of the spine, 18; dorsal region, 8; cervical region, 3; femur, 19; skull, 11; ribs, 11; sternum, 9; clavicle, 4; tibia, 4; humerus, 4; scapula, 3; os calcis, radius and maxilla, 1 each. Striking symptomatic relief, especially from pain, was obtained by roentgen therapy in small divided daily exposures of from 200 to 300 roentgens (measured in air) with total doses of from 600 to 1,200 roentgens per portal.

In Herscher's [186] case the major involvement was in the bone marrow, without apparent involvement of lymph nodes. The clinical course was acute, with death three months after the onset of the symptoms (weakness and backache).

Pulmonary involvement in Hodgkin's disease was noted in 37.6 per cent of 29 patients in Falconer and Leonard's [187] series. Five of 7 patients showed pleural effusion. Pleural lesions were present in 3 patients at autopsy.

Among the complications of lymphoblastoma which point the way to therapy, Desjardins, Habein and Watkins [188] enumerated fever; pruritis; discrete or diffuse infiltration of the skin, with or without pruritis; infiltration of the periocular tissues or eyelids, with or without impairment of vision; erosion or necrosis of the sternum from enlarging mediastinal lymph nodes; pressure injury of the recurrent laryngeal nerve; pleural effusion from mediastinal obstruction; ascites from enlarged mesenteric or retroperitoneal nodes; edema of the legs from pressure on the inguinal or iliac nodes; infiltration of the testis; involvement of bone by direct erosion or invasion of bone marrow; infiltration of the spinal canal, spinal cord or brain, and secondary infection. Desjardins and his associates [188] warned against the use of maximal doses of x-rays and said they obtained satisfactory results with rays generated at 150 kilovolts (peak) instead of 200 kilovolts.

Certain differential features between Hodgkin's disease, lymphosarcoma and aleukemic lymphadenosis were considered in Held and Goldbloom's [189] study of lymphadenopathy.

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185. Dresser, R., and Spencer, J.: Hodgkin's Disease and Allied Conditions of Bone, Am. J. Roentgenol. **36**:809, 1936.

186. Herscher, H.: Hodgkin's Disease of Bone Marrow and Liver Without Apparent Involvement of Lymph Nodes, Am. J. Roentgenol. **35**:73, 1936.

187. Falconer, E. H., and Leonard, M. E.: Hodgkin's Disease of the Lung, Am. J. M. Sc. **191**:780, 1936.

188. Desjardins, A. U.; Habein, H. C., and Watkins, C. H.: Unusual Complications of Lymphoblastoma and Their Radiation Treatment, Am. J. Roentgenol. **36**:169, 1936.

189. Held, I. W., and Goldbloom, A. A.: Adenopathy: Discussion of Differential Diagnosis Between Hodgkin's Disease, Lymphosarcoma and Aleukemic Lymphadenosis, Internat. Clin. **3**:70, 1936.

In studying patients with Hodgkin's disease, Rosenthal[190] found that those in whom there was a predominance of lymphocytes in the glands showed an average duration of life after the onset of the disease of four and thirty-five hundredths years; those in whom the lymphocytes were moderately reduced, two and twenty-nine hundredths years, and those in whom the lymphocytes were practically absent, one and fourteen hundredths years. A progressive disappearance of lymphocytes characterizes the disease, whether roentgen therapy is used or not. In Raagaard's[191] series of 12 male and 7 female patients the average duration was about sixteen months (one to sixty-four months). He found that in a patient who had had the disease for six years repeated recurrences in the mediastinum were always alleviated by irradiation, which did not appear to decrease in effectiveness.

Watt,[192] in a study of 201 cases of Hodgkin's disease over a decade, recommended high voltage roentgen therapy spread over a period of from a week to a month. Recrudescences are to be treated at the earliest possible moment. Pyrexia is usually associated with an active focus. Arsenic should not be used for six weeks after roentgen therapy. Periodic inspection of patients is advisable.

That syphilis may simulate Hodgkin's disease clinically was noted by Clodfelter.[193]

In Chevallier and Gorse's[194] patient tuberculosis of the lymph nodes was first noted, but three years later Hodgkin's disease had developed. There was a good response to roentgen therapy. In Funshteyn's[195] patient also there was a combination of the two diseases. The patient reported on by Hernández, Yrigoyen and Guastavino's[196] showed generalized lymphogranulomatosis, with the lesions simulating tuberculosis of the lung, pleura and lymph nodes.

The localization of lymphogranuloma may give rise to specific symptoms as well as cause confusion in diagnosis, as when nodules or cavity

190. Rosenthal, S. R.: Significance of Tissue Lymphocytes in Prognosis of Lymphogranulomatosis, Arch. Path. **21**:628 (May) 1936.

191. Raagaard, O.: Nineteen Cases of Lymphogranulomatosis (Sternberg), Ugesk. f. læger **98**:759 (Aug. 13) 1936.

192. Watt, W. L.: Hodgkin's Disease and Deep X-Ray Therapy, Brit. M. J. **2**:712 (Oct. 10) 1936.

193. Clodfelter, H. M.: Syphilis Presenting Clinical Picture of Hodgkin's Disease, Arch. Dermat. & Syph. **33**:535 (March) 1936.

194. Chevallier, P., and Gorse, J.: Maladie de Hodgkin ayant commencé par une adénopathie tuberculeuse du cou, Sang **10**:894, 1936.

195. Funshteyn, L.: Lymphogranulomatose und Tuberkulose: Klinische Untersuchung, Beitr. z. Klin. d. Tuberk. **88**:41, 1936.

196. Hernández, I. M.; Yrigoyen, L., and Guastavino, C. R.: Pseudo tuberculosis ganglio-pleuro-pulmonar por granulomatosis generalizada, Arch. de tisiol. **12**:21, 1936.

formation appears in the lungs. The bone lesions may be osteoclastic or osteoblastic and sclerosing, with periosteal osseous formations. A new sign of unfavorable progress is a peculiar fair transparent complexion with red cheeks in a patient with multiple lymphomas. For treatment, a single dose of from 100 to 200 roentgens is given every day or every other day until from 1,000 to 1,400 roentgens have been given over the glands, lungs, spleen and bone lesions (Ebbehøj [197]).

Lymphosarcoma, or Hodgkin's disease, may first appear in the abdominal, mediastinal or inguinal nodes rather than primarily in the neck, with subsequent spread to other regions. Symptoms of abdominal lymphomatosis are nausea, vomiting, increasing constipation and distention with gas. Pain may be in the back or sides or legs, with obstructive edema. Fever and pruritis are important symptoms. Maximum doses of roentgen rays are to be avoided, and the highest kilovoltage is not necessarily desirable. Desjardins and Watkins [198] recommended repeated treatment at regular intervals of three or four weeks, unless pronounced leukopenia contraindicates this course.

From a study of cases and reviews of published data Ginsburg [199] was unable to find clearcut criteria for the absolute differentiation of Hodgkin's disease and lymphosarcoma. "Hodgkin's disease," he summarized, "varies in no fundamental clinical characteristics from lymphosarcoma. Whatever clinical variations it may present at times are merely variations that one may encounter in any disease affecting different individuals under different constitutional and environmental conditions."

Chapman,[200] on the other hand, on the basis of Gordon's test, expressed the belief that Hodgkin's disease is a separate clinical and pathologic entity, distinct from lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and lymphoblastoma of undetermined types. Gordon's test, which consists of the intracerebral injection into rabbits of a saline emulsion of Hodgkin's tissue, and the observation for ataxia, spasm and paralysis, gave negative results in 64 of 65 controls. In 9 of 16 cases of Hodgkin's disease at least 1 rabbit gave a positive reaction, although 1 or more rabbits failed to give a reaction in 5 of the 9.

197. Ebbehøj, K.: Lymphogranulomatosis, Hospitalstid. **79**:253 (March 17) 1936.

198. Desjardins, A. U., and Watkins, C. H.: Abdominal Lymphoblastoma and Its Treatment by Irradiation, South. M. J. **29**:344, 1936.

199. Ginsburg, S.: Lymphosarcoma and Hodgkin's Disease: Clinical Characteristics, Ann. Int. Med. **10**:337, 1936.

200. Chapman, Earle M.: Studies in Hodgkin's Disease: Clinical Application of the Gordon Test (a Syndrome of Ataxia, Spasm and Paralysis Induced in Rabbits by the Intracerebral Injection of Emulsified Hodgkin's Tissue), Ann. Int. Med. **10**:742, 1936.

The test then shows some specificity for Hodgkin's disease but is not always correct in known cases.

Applying Gordon's test, Goldstein [201] obtained positive responses with material from nine lymphogranulomatous nodes. In the two tests which gave negative results, both in established cases of Hodgkin's disease, all inoculated animals remained free from the encephalitic syndrome. All control groups (twenty, including five tuberculous glands and two from patients with infectious mononucleosis) gave negative results.

For diagnosis Emile Weil, Isch-Wall and Perlès [202] used lymph gland puncture. Endothelial elements and giant cells of Sternberg are diagnostic features. In some types there is an increase in the number of monocytes or eosinophils or massive infiltration with polymorphonuclear cells. In the advanced stages fibrous tissue predominates.

Sailer [203] studied Hodgkin's disease in a man aged 77 years and noted that the disease did not differ essentially from that in younger patients.

Jörg [204] summarized the general pathologic picture of Hodgkin's disease and reviewed the recent literature on the subject.

Gordon's test for Hodgkin's disease gave positive results in 2 cases in Rosenberg and Bloch's [205] series during early stages, but negative results in a case of chronic involvement of a year's duration. These authors described the technic and reviewed the literature on the subject. When a positive result is obtained the rabbits into which the gland emulsion has been injected intracerebrally show symptoms after an incubation period of from two to six days (maximum, sixteen days). Ataxia, staggering, falling, retraction of the head, opisthotonos, convulsive movements, nystagmus, grinding of the teeth, urinary and fecal incontinence, progressive wasting and weakness affecting particularly the hind quarters. Death may follow in from three days to a month, or recovery or a chronic state may supervene.

Injection of saline emulsions of glands involved by Hodgkin's disease into the lymphatic glands of the paws of dogs did not cause the

201. Goldstein, J. D.: The "Gordon Test" for Hodgkin's Disease, Am. J. M. Sc. **191**:775, 1936.

202. Weil, P. E.; Isch-Wall, P., and Perlès, S.: Le diagnostic de la maladie de Hodgkin par la ponction des ganglions, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1006 (June 22) 1936; Presse méd. **44**:1540 (Oct. 3) 1936.

203. Sailer, S.: Hodgkin's Disease in the Aged, Am. J. Clin. Path. **6**:241, 1936.

204. Jörg, M. E.: La anatomía patológica general de la granulomatosis maligna de Hogkin-Paltauf y Sternberg (conceptos actuales, nueva bibliografía), Semana méd. **1**:1741 (June 4) 1936.

205. Rosenberg, D. H., and Bloch, L.: The Gordon Test for Hodgkin's Disease, J. A. M. A. **106**:1156 (April 4) 1936.

development of the disease after from seven months to three years (Chapman [206]).

Slight leukocytosis was noted by Roth and Watkins [207] in cases of Hodgkin's disease of between one and two years' duration. Polymorphonuclear neutrophils were slightly increased in number after six months, with a slight relative decrease in the number of lymphocytes. Monocytes tend to be more mature than in the average normal person. These tendencies are not more marked when there is extensive involvement of the body. The author concluded: "There is no specific change in the blood picture which is diagnostic of Hodgkin's disease."

Wiseman [208] claimed that the majority of patients with Hodgkin's disease have a normal or low leukocyte count. There is a tendency to neutrophilia (5,000 or more neutrophils per cubic millimeter); at least two thirds of his patients showed no increase in the number of eosinophils. Definite lymphopenia was characteristic (less than 1,500 lymphocytes per cubic millimeter), with monocytosis (700 monocytes per cubic millimeter), giving a high monocyte-lymphocyte ratio (1:33).

Peirce, Jacox and Hildreth [209] studied the records of 214 patients with Hodgkin's disease and noted that the clinical symptoms and signs and the changes in the character of the blood often suggest the disease. They are not indicative of the extent of the intrathoracic involvement. In two thirds of the patients roentgen examination of the chest revealed the diagnosis and extent of the disease.

From a survey of the clinical results of roentgen treatment of 161 patients with Hodgkin's disease, Jacox, Peirce and Hildreth [210] concluded that this type of therapy induced definite extension of life as compared with the results for patients who did not receive this treatment. "Systemic irradiation," they said, "has been no more effectual than repeated local irradiation in prolongation of the total duration of the disease in those cases now known to have died." They advocated systemic irradiation of all lymphatic areas.

206. Chapman, E. M.: Studies in Hodgkin's Disease: Unsuccessful Experiments to Transmit Hodgkin's Disease to Dogs by Intralymphatic Injection, Proc. Soc. Exper. Biol. & Med. **33**:572, 1936.

207. Roth, G. M., and Watkins, C. H.: The Leukocyte Picture in Hodgkin's Disease, Ann. Int. Med. **9**:1365, 1936; Proc. Staff Meet., Mayo Clin. **11**:593 (Sept. 16) 1936.

208. Wiseman, B. K.: Lymphopoiesis, Lymphatic Hyperplasia, and Lymphemia: Fundamental Observations Concerning the Pathologic Physiology and Interrelationships of Lymphatic Leukemia, Leukosarcoma and Lymphosarcoma, Ann. Int. Med. **9**:1303, 1936.

209. Peirce, C. B.; Jacox, H. W., and Hildreth, R. C.: Roentgenologic Considerations of Lymphoblastoma: Roentgen Pulmonary Pathology of the Hodgkin's Type, Am. J. Roentgenol. **36**:145, 1936.

210. Jacox, H. W.; Peirce, C. B., and Hildreth, R. C.: Roentgenologic Considerations of Lymphoblastoma: Roentgen Therapy of Hodgkin's Disease, Am. J. Roentgenol. **36**:165, 1936.

The survival period after roentgen therapy in O'Brien's [211] series averaged fourteen and two-fifths months. Anemia is a greater source of potential danger after teleoroentgen therapy than after local treatment. O'Brien stated:

> The obvious direct benefits from roentgen therapy are decrease in the size of the liver and spleen, with consequent relief from pressure symptoms, resorption of pleural effusion, resorption of ascites, relief of pain, restoration of sensibility of locomotion in cord and vertebral metastases, increase in red cells and color index, remissions of the disease with return to occupation, and comparative comfort over long periods of time.

Lymphosarcoma of the intestine usually does not cause constriction but more often produces sacculation. In Greenfield's [212] case the diagnosis was made preoperatively on the basis of the roentgenographic changes. After high voltage roentgen therapy an excellent remission was produced.

Various aspects of Hodgkin's disease and related diseases have been emphasized in recent reports: cutaneous involvement (Arzt [213]), involvement of the scalp (Wrong [214]), involvement of the orbit (Kyrieleis [215] and Muscatello [216]), primary localization in the nasopharynx (Berendes [217]), elephantiasis of the penis and scrotum (Sánchez-Covisa and de la Cuesta [218]), hemolytic jaundice (Fortunato [219]), localization in the thyroid region simulating thyroid adenoma (Presno y Bastiony [220]), localization in the mediastinum (Medoc and Marcos [221]) and primary involvement of the tonsil (Wullstein [222]).

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211. O'Brien, F. W.: Roentgen Treatment of the So-Called Malignant Lymphomas, J. A. M. A. **107**:2022 (Dec. 19) 1936.

212. Greenfield, H.: Early Roentgen Diagnosis of Jejunal Lymphosarcoma: Report of Case, Am. J. Roentgenol. **36**:674, 1936.

213. Arzt, L.: Zur Kenntnis der Lymphogranulomatosis cutis (Paltauf-Sternberg), Wien. med. Wchnschr. **86**:677 (June 20) 1936.

214. Wrong, N. M.: Hodgkin's Disease of the Scalp: Report of a Case, Arch. Dermat. & Syph. **33**:259 (Feb.) 1936.

215. Kyrieleis, W.: Ueber Augenhintergrundsveränderungen bei Lymphogranulomatose, Ztschr. f. Augenh. **89**:193, 1936.

216. Muscatello, F.: Lipogranulomatosi dell' orbita, Rassegna ital. d'ottal. **5**: 108, 1936.

217. Berendes, J.: Der Epipharynx als primärer Sitz der Lymphogranulomatose, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **141**:141, 1936.

218. Sánchez-Covisa, J., and de la Cuesta, L.: Elefantiasis peneoescrotal en el curso de linfogranulomatosis maligna de Paltauf-Sternberg, Actas dermo-sif. **28**:734 (May) 1936.

219. Fortunato, A.: Morbo di Hodgkin con ittero emolitico, Studium **26**: 147 (July 1) 1936.

220. Presno y Bastiony, J. A.: Enfermedad de Hodgkin de localizacíon primitiva en la región tiroidea simulando un bocio, Rev. de med. y cir. de la Habana **41**:213 (April 30) 1936.

(Footnotes continued on next page)

Gordon [223] and Warner [224] experimented with vaccine therapy for Hodgkin's disease.

LEUKEMIA

The outpouring of immature cells of all types in leukemia was shown in the cases of 2 patients characterized by Campbell, Henderson and Croom [225] as demonstrating a mixed monocytic-myeloid reaction. While the monocytes predominated in the blood, both monocyte and myeloid cells were present in the tissues in about equal proportions. The process was interpreted as a "stem cell" hyperplasia with simultaneous differentiation into two distinct cell types. Both patients showed necrotic ulceration at the anorectal region, and 1 showed a localized tumor in the cecum and appendix.

The coincidental occurrence in the same patient of pernicious anemia (macrocytosis, reticulocyte response to liver extract, achlorhydria, reduced gastric secretion, loss of vibratory sense and degeneration of the posterior and lateral columns of the spinal cord) and of lymphatic leukemia (splenomegaly, lymphadenopathy and leukocytosis—330,000 leukocytes per cubic millimeter, with a predominance of lymphocytes) has been reported by Rich and Schiff.[226] A somewhat similar situation was presented by Duthoit and Houcke's [227] patient with "subleukemic lymphatic leukemia" and a myeloid reaction, with megaloblasts and a color index of 1.34.

Krumbhaar [228] suggested the term lymphomatoid diseases for the heterogeneous group of conditions classified as lymphoblastoma, limiting the latter term to "a tumor derived from the lymphoblast." In comparing the weight of the spleen in different types of leukemia, the average was as follows: acute lymphatic, 693.5 Gm.; chronic lymphatic,

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221. Medoc, J., and Marcos, J. R.: Un caso de linfogranulomatosis solitaria del mediastino; estudio clínico y anatomopatológico, An. Fac. de med. de Montevideo **20**:319, 1935.

222. Wullstein, H.: Ueber beginnende Lymphogranulomatose mit Primärinfekt an der Gaumenmandel und ihre Behandlung, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **141**:146, 1936.

223. Gordon, M. H.: Aetiology of Lymphadenoma: Sensitized Vaccine of Elementary Bodies, Lancet **2**:65 (July 11) 1936.

224. Warner, E. C.: Treatment of Lymphadenoma, with Sensitised Vaccine of Elementary Bodies, Lancet **2**:417 (Aug. 22) 1936.

225. Campbell, A. C. P.; Henderson, J. L., and Croom, J. H.: Monocytic Leukaemia with Myeloid Hyperplasia and Localised Tumour Formation, J. Path. & Bact. **42**:617, 1936.

226. Rich, M. L., and Schiff, L.: A Case of Pernicious Anemia and Chronic Lymphatic Leukemia, Ann. Int. Med. **10**:252, 1936.

227. Duthoit, A., and Houcke, E.: Subleucémie lymphoïde avec anémie mégaloblastique et réaction myéloïde, Sang **10**:252, 1936.

228. Krumbhaar, E. B.: The Lymphomatoid Diseases (the So-Called Lymphoblastomas), J. A. M. A. **106**:286 (Jan. 25) 1936.

1,297.5 Gm.; acute myelogenous, 482.2 Gm., and chronic myelogenous, 1,879.2 Gm. Among the patients with myelogenous leukemia, spleens weighing from 4,930 and 5,380 Gm. were encountered, and among the patients with lymphatic leukemia there was one of 4,400 Gm.

A case of acute leukemia which first became manifest after treatment with a radio-active solution has been described by Rimbaud, Anselme-Martin, Lafon and Castagné.[229] Reports of cases emphasizing involvement of the liver and spleen (Cabot case 22,282 [230]) as well as absence of splenomegaly (Legrand [231]) have been published. Marcus [232] described the case of a patient who had a long remission in the course of acute aleukemic leukemia. In Zemplén's [233] patient the disease started as acute myeloblastic leukemia and developed into chloroma. Cutaneous involvement was noted in a patient by Goldhamer and Barney,[234] and they reviewed the findings in 16 other similar cases reported in the literature. The appearance of cutaneous nodular infiltrations suggests a bad prognosis, as death followed in from fifteen days to four months in this group. The nodules vary in diameter from about 2 to 20 mm., and the color is that of normal skin or various depths of purple. The most common sites are the skin of the trunk, the anterior surface of the chest, the extremities and rarely the face and mucous membranes. Zimmerman and Curtis [235] described the cutaneous nodules of a patient with myelogenous leukemia which progressed to the blast stage after leukopenia was induced by intensive roentgen therapy.

The problem of the differential diagnosis of marked eosinophilia and eosinophilic leukemia was presented in a case described by Lottrup.[236] The leukocyte count was 13,800 per cubic millimeter, with 54 per cent eosinophils. The diagnosis of eosinophilic bronchitis was made rather than leukemia, because of the sparsity of immature forms.

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229. Rimbaud, L.; Anselme-Martin, G.; Lafon, R., and Castagné, R.: Leucémie aiguë en concomitance avec un traitement radio-actif suivi sans contrôle médical, Arch. Soc. d. sc. méd. et biol. de Montpellier **17**:118, 1936.

230. Aleukemic Myeloid Leukemia with Involvement of Liver and Spleen, Cabot Case 22282, New England J. Med. **215**:91 (July 9) 1936.

231. Legrand, R.: Leucémie myéloïde sans splénomégalie, Echo méd. du Nord **5**:858 (May 24) 1936.

232. Marcus, I. H.: Complete Temporary Recovery of Long Duration, in Acute Aleucemic Myeloid Leucemia: Case Report, J. Lab. & Clin. Med. **21**:1006, 1936.

233. Zemplén, B.: Ein im Bilde einer akuten Myeloblasten-Leukämie beginnendes Chlorom, Folia haemat. **55**:262, 1936.

234. Goldhamer, S. M., and Barney, B. F.: Myelogenous Leukemia with Cutaneous Involvement, J. A. M. A. **107**:1041 (Sept. 26) 1936.

235. Zimmerman, E. F., and Curtis, H. C.: Aleukemic Myelosis with Cutaneous Nodules, Arch. Dermat. & Syph. **33**:684 (April) 1936.

236. Lottrup, M. C.: Hochgradige Eosinophilie und eosinophile Leukämie, Folia haemat. **54**:66, 1935.

Among the less common types of leukemia is an example of an acute basophilic form described by Groat, Wyatt, Zimmer and Field.[237] Their patient had a leukocyte count varying from 40,000 to 121,000 per cubic millimeter, with basophils constituting from 21 to 61 per cent of the cells. There were progressive anemia, thrombopenia and abnormal platelets. The sternal bone marrow showed many basophils, with immature forms, although the neutrophils were apparently normal. There was a progressive increase in the number of myeloblasts (24,000). Roentgen therapy was of help early in the disease. Symptomatic improvement followed blood transfusions. The total duration of the disease was about eight months, with death from bronchopneumonia. Duodenal ulcers complicated the picture.

A second unusual type was noted by Patek and Castle [238] in a woman of 60 years who showed plasma cell leukemia. Eleven similar cases were noted in the literature. The leukocyte count varied from 21,800 to 50,100 per cubic millimeter, with from 27 to 43 per cent of the cells belonging to the plasma cell group. There was progressive anemia, and death resulted from bronchopneumonia. The pathologic picture of this condition has been described by Jores and Bruns,[239] who characterized the lesion as malignant plasmoma. In this patient, a 64 year old woman, the leukocyte count rose to 38,000 per cubic millimeter, with 45 per cent plasma cells. There was a multiple myeloma made up of plasma cells.

Additional cases of megakaryocytic leukemia (an aleukemic form with enlargement of the liver and spleen) have been recorded by Chini,[240] Emile Weil, Isch-Wall, Perlès and Scemama [241] and Introzzi.[242]

A case of myelogenous leukemia in a woman with a red blood cell count of 5,500,000, a leukocyte count of from 22,000 to 33,000 and a platelet count of more than 2,500,000 per cubic millimeter was reported by Drake.[243] In discussing this case Dameshek [244] said that the diagnosis should have been polycythemia, as he has noted high platelet counts

237. Groat, W. A.; Wyatt, T. C.; Zimmer, S. M., and Field, R. E.: Acute Basophilic Leukemia, Am. J. M. Sc. **191**:457, 1936.

238. Patek, A. J., Jr., and Castle, W. B.: Plasma Cell Leukemia: Consideration of the Literature with Report of a Case, Am. J. M. Sc. **191**:788, 1936.

239. Jores, A., and Bruns, W.: Ein Fall von "malignem Plasmom" mit einen Beitrag zur sog. "Plasmazellenleukämie," Folia haemat. **55**:227, 1936.

240. Chini, V.: La mielosi aleucemica megacariocitaria, Policlinico (sez. med.) **43**:257, 1936.

241. Weil, P. E.; Isch-Wall, P.; Perlès, S., and Scemama, J.: Un cas de splénomégalie myéloïde megácaryocytaire, Sang **10**:797, 1936.

242. Introzzi, P.: Contributo allo studio della patologia del sistema megacariocitico (megacariociti nel sangue periferico di anemia perniciosa progressivae di leucemia acuta emocitoblastica), Haematologica **16**:217, 1935.

243. Drake, C. B.: Leukemia with Thrombocytosis, J. A. M. A. **106**:1005, (March 21) 1936; **107**:446 (Aug. 8) 1936.

244. Dameshek, W.: Leukemia or Polycythemia, J. A. M. A. **106**:1837 (May 23) 1936.

in that disease. Kugelmass [245] claimed that in this case it was not justifiable to make a diagnosis of latent leukemia on the basis of a high platelet count alone, as secondary thrombocythemia may be present in polycythemia, lymphogranulomatosis, chronic myelosis, splenic dysfunction and injury to the tissues by severe infection or surgical trauma. Subsequent study confirmed the diagnosis of leukemia. The case is interesting as it brings out many difficulties in the diagnosis of conditions in which intensive stimulation of the bone marrow is a factor.

Hyperproteinemia and hypereuglobulinemia with the secretion of Bence-Jones' protein in the urine characterized Keilhack's [246] case of aleukemic myelogenous leukemia. A relationship to the myelomas was suggested, and other diseases in which these symptoms appear were analyzed.

The fever in leukemia, according to Vlados,[247] is the result of the disturbed purine metabolism.

In acute "blast" leukemia (lymphatic) Arneth [248] noted a relative predominance of oval blood platelets, 2.5 microns in diameter, with an absolute decrease in the number of larger and of elongated forms. This tendency was less marked in cases of chronic lymphatic leukemia.

Hepatic infarction may be a complication of chronic myelogenous leukemia (Morgan, Lieber and Stewart [249]).

Leukemic cells from old mice have a lower rate of metabolism than those from younger mice. When cells from either group were inoculated into the other, the resulting leukemic cells assumed a rate more nearly comparable to the age of the host. "Host age," commented Victor and Potter,[250] "does not modify the inherent constitution of the leukemia cells but acts as a determining environmental factor on their metabolism."

In a strain of pure albino rats Wilens and Sproul [251] noted the spontaneous development of leukemia in 3.3 per cent of the animals (myeloid, 7 cases; chloromyeloid, 4 cases, and lymphatic, 1 case). The

245. Kugelmass, I. N.: Leukemia with Thrombocytosis, J. A. M. A. **106**:1588 (May 2) 1936.

246. Keilhack, H.: Die Hyperproteinämie und Hypereuglobulinämie als Symptome einer chronischen aleukämischen Myelose, Folia haemat. **55**:406, 1936.

247. Vlados, C.: Sur la genèse de l'état fébrile chez les malades atteints de leucémie, Sang **9**:961, 1935.

248. Arneth, J.: Ueber das qualitative Thrombocytenblutbild bei der lymphatisch-leukämischen Reaktion (Leukämie) auf Grund von 30 Beobachtungen, Folia haemat. **56**:49, 1936.

249. Morgan, D. R.; Lieber, M. M., and Stewart, H. L.: Hepatic Infarction in Myelogenous Leukemia and Periarteritis Nodosa, Am. J. M. Sc. **192**:540, 1936.

250. Victor, J., and Potter, J. S.: Host Age and Cell Metabolism in Mouse Lymphatic Leukemia, Proc. Soc. Exper. Biol. & Med. **33**:609, 1936.

251. Wilens, S. L., and Sproul, E. E.: Spontaneous Leukemia and Chloroleukemia in the Rat, Am. J. Path. **12**:249, 1936.

ages varied from 18 months to 2 years. There were 8 males and 4 females. In the rats with chloroleukemia the tumors were greenish, the pigment resembling that of human beings with chloroma.

Wiseman [208] concluded that lymphatic leukemia may be either neoplastic or metabolic; in the majority of cases chronic lymphatic leukemia is of the latter type. The metabolic derangement was postulated as being similar to the mechanism which produces pernicious anemia. Wiseman, Doan and Erf [252] claimed that the anemia in lymphatic leukemia is due not to the crowding out of erythroblastic tissue from the marrow but to an effect of increased volume of lymphatic tissue elsewhere in the body. Myelopoiesis, they concluded, is metastatic when it occurs in lymph nodes. Myeloid or lymphoid hyperplasia occurs at the expense of the hypoplasia of the other.

To support the theory of the local origin of hemocytoblastic growths, as opposed to the metastatic concept, Smith and Silberberg [253] presented a patient with multiple myeloma in whom there were undifferentiated or partly differentiated blood cells (proerythroblasts and other immature red blood cells, lymphocytes, plasma cells and megakaryocytes).

Articular manifestations in leukemia are not uncommon (Krafft [254]), and the syndrome may simulate acute rheumatism and Still's disease (Conybeare [255]). Erythroderma was the initial and, for a time, the only clinical manifestation of subacute leukemia (blast) in a patient described by Margarot, Rimbud and Roche.[256]

Rigler [257] reported the appearance of "enormously enlarged gastric rugae, resembling the convolutions of the brain" in a patient with a basal cell carcinoma of the skin and leukemic infiltration of a cervical lymph node and of the skin. The blood was not abnormal. Improvement followed roentgen therapy. The roentgenographic appearance of the stomach is not specific, however, but may be similar to that seen in chronic hypertrophic gastritis. The latter condition is not improved by roentgen therapy.

252. Wiseman, B. K.; Doan, C. A., and Erf, L. A.: A Fundamental Reciprocal Relationship Between Myeloid and Lymphoid Tissues: Its Recognition, Nature, and Importance as Revealed by Experimental and Clinical Studies, J. A. M. A. **106**: 609 (Feb. 22) 1936.

253. Smith, R. P., and Silberberg, M.: Multiple Myeloma of Hemocytoblastic Type, Arch. Path. **21**:578 (May) 1936.

254. Krafft, J.: Leukämische Gelenksymptome im Kindesalter, Kinderärztl. Praxis **7**:295 (July) 1936.

255. Conybeare, E. T.: Case of Leukaemia Simulating Acute Rheumatism and Still's Disease, Guy's Hosp. Rep. **86**:343, 1936.

256. Margarot, J.; Rimbaud, P., and Roche, J.: Erythrodermie constituant la manifestation clinique initiale et pendant quelque temps, exclusive d'une leucémie à éléments primordiaux et d'évolution subaiguë, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Lyon) **42**:1503, 1935.

257. Rigler, L. G.: Leukemia of the Stomach Producing Hypertrophy of the Gastric Mucosa, J. A. M. A. **107**:2025 (Dec. 19) 1936.

The neucleotide nitrogen content of the blood of patients with leukemia is high. For normal males the amount is 6.2 mg. and for females 5.2 mg. per hundred cubic centimeters. The average for 10 males with myelogenous leukemia with an elevated leukocyte count was 7.36 mg. and for 5 females 5.84 mg. per hundred cubic centimeters. In normal persons and in patients with aleukemic leukemia the nucleotide nitrogen is more closely correlated with the red blood cell count (Allen, Lucia and Eiler [258]).

Certain chemical differences in the composition of the white blood cells in leukemia, especially in the lipid fraction, were noted by Boyd.[259] In 9 patients with chronic myelogenous leukemia the values for total lipids, total fatty acids, total cholesterol, free cholesterol and phospholipid were greater than normal, as compared with the condition in 8 patients with chronic lymphatic leukemia, for whom the amounts were less than normal. The amount of neutral fat was slightly increased in lymphatic leukemia, but in both types the ester cholesterol content was less than normal. In a patient with "acute myeloid leukemia" the leukocyte lipid content was relatively low, whereas in 2 patients with Hodgkin's disease it was relatively high.

Fiessinger and Laur [260] reported that they had under their care a 51 year old patient known to have had lymphatic leukemia for twenty years. He had had roentgen therapy at times. The blood was going into the blast stage, with a leukocyte count of 208,000 per cubic millimeter.

The occurrence of localized leukemic infiltrations was pointed out by Cleland,[261] and the resemblance to lymphosarcoma and pseudoleukemia was noted. Patients with infiltration in the cardiac muscle, kidneys, pancreas, brain and other organs were cited, showing the specific symptomatology which these tumors may cause.

Craver [262] commented on the great variation and severity of symptoms in different patients with leukemia. A long duration is more common in lymphatic than in myelogenous leukemia. There are certain features which suggest a relationship between leukemia and Hodgkin's disease, lymphosarcoma and erythremia. Lymphosarcoma may terminate with a leukemic syndrome, as noted in the patient of Morin,

258. Allen, F. W.; Lucia, S. P., and Eiler, J. J.: Nucleotide Nitrogen Content of Pathologic Human Whole Blood, J. Clin. Investigation **15**:157, 1936.

259. Boyd, E. M.: The Lipid Composition of the White Blood Cells in Leukemia, Arch. Path. **21**:739 (June) 1936.

260. Fiessinger, N., and Laur, C. M.: Leucémie lymphatique splénique pure d'une durée de 20 ans et encore en traitement, Sang **10**:743, 1936.

261. Cleland, J. B.: Leukaemic Infiltrations, Brit. M. J. **2**:1191 (Dec. 21) 1935.

262. Craver, L. F.: Clinical Manifestations and Treatment of Leukemia, Am. J. Cancer **26**:124, 1936.

Lemieux and Leblond.[263] Lymphosarcoma of the mediastinum was the primary clinical lesion. Wiseman[264] also discussed this phase of lymphosarcoma.

A detailed account of a patient with chronic myelogenous leukemia and painful priapism was given by Denéchau.[265] This complication, although frequently mentioned in accounts of leukemia, is relatively rare. In this case there was improvement after intensive irradiation over the pelvis and spleen.

In a patient with lymphatic leukemia, severe leukopenia (200 to 800 leukocytes per cubic millimeter) developed after roentgen therapy. The initial white blood cell count was 70,200 per cubic millimeter. The patient received nine treatments within thirty-five days, totaling probably more than 5,500 roentgens, over different parts of the body. The polymorphonuclear leukocyte count was reduced to 5 per cent ("agranulocytosis"). After therapy with pentose nucleotide, Fiessinger and Boudin[266] found an increase in the total leukocyte count, with a slight increase in the number of polymorphonuclears. Death followed in two months.

Lazeanu and Saragea[267] studied a patient with chronic lymphatic leukemia for whom the leukocyte count was 2,500,000 per cubic millimeter, over 96 per cent of the cells being lymphocytes. The count was reduced to 1,000,000 per cubic millimeter with roentgen therapy. (Other authors have reported counts of from 1,500,000 to 2,000,000 per cubic millimeter.)

The basal metabolic rate parallels the clinical condition of the patient more closely than the blood count, although this is not infallible, concluded Middleton, Meyer and Pohle[268] from a careful study of 21 patients with leukemia.

The coincidental occurrence of carcinoma (cutaneous) and lymphatic leukemia in the same patient has been described by Pulvertaft.[269] He

263. Morin, E.; Lemieux, R., and Leblond, S.: Syndrome leucémique au cours d'un lymphosarcome du médiastin, Laval méd. **1**:24, 1936.

264. Wiseman, B. K.: The Blood Pictures in the Primary Diseases of the Lymphatic System: Their Character and Significance, J. A. M. A. **107**:2016 (Dec. 19) 1936

265. Denéchau, D.: Un nouveau cas de priapisme révélateur d'une leucémie myéloïde. Résultats heureux et prolongés du traitement radiothérapique, Sang **10**:86, 1936.

266. Fiessinger, N., and Boudin, G.: Aleucie hémorragique et agranulocytose après un traitement radiothérapique, au cours d'une leucémie lymphoïde splénomégalique, Sang **10**:377, 1936.

267. Lazeanu, E., and Saragea, T.: Leucémie lymphatique avec un très grand nombre de leucocytes dans le sang, Sang **10**:123, 1936.

268. Middleton, W. S.; Meyer, O. O., and Pohle, E. A.: Influence of Roentgen Therapy upon Basal Metabolism in Leukemia, Radiology **26**:586, 1936.

269. Pulvertaft, R. J. V.: Multiple Primary Epithelioma in Lymphatic Leukaemia, Brit. J. Surg. **24**:50, 1936.

commented on the fact that lymphocytes have been considered as a protective barrier against the spread of tumors. Similarly, a patient may have miliary tuberculosis and leukemia (Harbitz [270]). It is suggestive that the leukemic cell differs in its functional possibilities from the normal lymphocyte.

From a study of patients with acute leukemia Jaffé [271] emphasized the excessive destruction of blood in some patients, with a compensatory reactive myelopoiesis. This results in the production of an increasing number of immature precursors of blood cells until the hemocytoblastic stage is reached.

Neumann and Neugebauer [272] described experiences in the giving of transfusions to leukemic patients which others no doubt have had. They noted the occurrence of reactions if the identical type of blood was not used, blood from group 0 donors causing reactions and hemolysis in all patients except those whose blood belonged to the same group.

Monocytic Leukemia.—Chini [273] described a patient showing a syndrome which is encountered occasionally among patients with pernicious anemia. His patient had a blood picture of pernicious anemia which later changed into that of monocytic leukemia. Splenomegaly was present, and marked megakaryocytosis was noted in the spleen. Kato [274] described a case of monocytic leukemia in an 18 month old infant.

Monocytic leukemia is described by some as a reticulo-endotheliosis (Reich [275]), acute histiocytic leukemia (Ramsey and Tank [276]) and aleukemic systemic endotheliosis (Fucci [277]), depending on the author's concept of the origin of the monocytes.

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270. Harbitz, F.: Acute Atypical Miliary Tuberculosis, i. e., Without Distinct Macroscopical Findings and Presenting Picture of Lymphatic Leucaemia, Acta path. et microbiol. Scandinav., supp. 26, 1936, p. 173.

271. Jaffé, R. H.: Nature of Anemia in Acute Leukemia, Arch. Path. **20**:725 (Nov.) 1935.

272. Neumann, W., and Neugebauer, W.: Scheinbare Blutgruppenänderung bei einem Leukämiekranken bei Unverträglichkeit von Blut eines sogenannten Universalspenders, Med. Klin. **32**:1067 (Aug. 7) 1936.

273. Chini, V.: Su di un caso complesso di emopatia (anemia a tipo pernicioso con splenomegalia; evoluzione leucemica a prevalente derivazione istioide e con spiccata megacariocitosi splenica), Arch. Ist. biochim. ital. **8**:127, 1936.

274. Kato, K.: Hematology and Pathology of Leucemic Reticuloendotheliosis (Monocytic Leucemia) Occurring in Eighteen-Month-Old Infant, J. Pediat. **8**: 679, 1936.

275. Reich, C.: Case of Aleucemic Reticuloendotheliosis, M. Rec. **144**:84 (July 15) 1936.

276. Ramsey, T. L., and Tank, R. A.: Acute Monocytic (Histiocytic) Leukemia, Ohio State M. J. **32**:637, 1936.

277. Fucci, N.: Sulle iperplasie del sistema reticolo-istiocitario: contributo allo studio della endoteliosi sistemica aleucemica, Minerva med. **2**:4 (July 7) 1936.

A case of monocytic leukemia together with its medicolegal features was discussed in *The Journal of the American Medical Association*.[278] A man with monocytic leukemia sustained an injury; gangrene of the leg and septicemia developed, and he died. In deciding the immediate cause of death and the financial responsibility, the court pointed out that under the Workman's Compensation Act, section 5223, "in case of aggravation of a pre-existing disease, compensation should be allowed only for such proportion of the disability or death due to the aggravation of such pre-existing disease as may be reasonably attributed to the injury on which the claim is based." Payment, then, was based on the shortening of the time that a patient with monocytic leukemia may be expected to live.

Among the various types of cells which may form a chloroma is the monocyte. A striking case was described by Gump, Hester and Lohr,[279] that of a man aged 55 years. The lesion produced marked exophthalmos, first unilateral, later bilateral. There was no marked improvement after roentgen irradiation. The leukocyte count varied from 15,000 to 26,000 per cubic millimeter, with from 20 to 62 per cent of the cells monocytes. There was a hemorrhagic tendency, with terminal pneumonia.

A case of monocytic leukemia in which cutaneous nodules were a feature has been described by Loveman.[280]

Leukemia in Children.—The subject of leukemia in children was studied by Pierce[281] (41 children, with 16 autopsies). For 48.7 per cent of the children there was a history of antecedent infectious illness from which there was failure to recover normally before the advent of the leukemic symptoms. Three types of patients were noted clinically: (1) those with a fulminating course and classic symptoms, (2) those with a less rapidly fatal course and with clinical and hematologic aspects which may be confused with leukemoid states or other blood dyscrasias and (3) those with a prolonged period of illness marked by relapses and remissions and a fluctuating blood picture. The aleukemic phase in this group of disorders may have certain clinical and pathologic features in common with those of malignant neutropenia.

An extensive review of acute leukemia in infants has been given by Lereboullet and Baize.[282]

278. Workmen's Compensation Acts: Death in Relation to Trauma and Preexisting Leukemia, Medicolegal Abstracts, J. A. M. A. **107**:308 (July 25) 1936.

279. Gump, M. E.; Hester, E. G., and Lohr, O. W.: Monocytic Chloroma (Reticulocytoblastoma with Monocytic Leukemia), Arch. Ophth. **16**:931 (Dec.) 1936.

280. Loveman, A. B.: Monocytic Leukemia Cutis: Report of a Case with Biopsy Studies, South. M. J. **29**: 357, 1936.

281. Pierce, M.: Childhood Leucemia, J. Pediat. **8**:66, 1936.

282. Lereboullet, P., and Baize, P.: La leucémie aiguë chez l'enfant, Sang **10**:279, 1936.

Morris and Hurwitz [283] noted the leukemic state in 2 infants who were convalescing from pertussis.

Differential Diagnosis.—In the differential diagnosis of leukemia and infectious mononucleosis, the absence of agglutination of sheep corpuscles by the patient's serum (so-called heterophile antibody test) is of great value if the patient has not had serum infection or serum sickness. Agglutination, in a dilution of 1:128, establishes a diagnosis of infectious mononucleosis. Kracke and Garver,[284] in pointing out this feature, also warned against confusing immature blast forms with lymphocytes.

Splenic puncture has been used by Emile Weil, Isch-Wall and Perlès [285] to diagnose cryptoleukemia. This is myeloid, lymphatic or leukoblastic leukemia in which the peripheral blood is essentially normal but in which the internal organs show the character of the disease.

Treatment.—The beneficial effects of potassium arsenite in chronic myelogenous leukemia have been studied by Stephens and Lawrence [286] in 7 patients. Solution of potassium arsenite U. S. P. was given rapidly in doses of from 10 to 30 or more drops a day until toxic symptoms appeared. The maintenance dose was as large as could be tolerated. Transfusions and roentgen therapy were used when indicated. The effects noted were (*a*) symptomatic improvement, (*b*) a reduction in the size of the spleen, (*c*) a decrease in the total white blood cell count, (*d*) a decrease in the number of immature cells and in the number of immature red blood cells in the peripheral blood, (*e*) an improvement in the anemia and (*f*) an increase in the number of platelets. The treatment may be continued indefinitely, but relapses may take place during the course of therapy.

Albuminuria in leukemia is favorably affected by roentgen irradiation, according to Solomon,[287] and he advised systematic irradiation of the kidneys before treatment of the spleen, bone marrow or glandular areas is begun.

No hematologic improvement was noted in leukemic patients by Meyer, Middleton and Thewlis [288] after the administration of beef lymph

283. Morris, M., and Hurwitz, S.: Myelogenous Leukemia in Infancy: Report of Two Cases Following Pertussis, Arch. Pediat. **53**:367, 1936.

284. Kracke, R. R., and Garver, H.: Laboratory Findings in Leukemic States, Am. J. M. Technol. **2**:81, 1936.

285. Weil, P. E.; Isch-Wall, P., and Perlès, S.: Les cryptoleucémies, Presse méd. **44**:41 (Jan. 8) 1936.

286. Stephens, D. J., and Lawrence, J. S.: The Therapeutic Effect of Solution of Potassium Arsenite in Chronic Myelogenous Leukemia, Ann. Int. Med. **9**:1488, 1936.

287. Solomon, I.: Ueber die Behandlung und Prognose der Leukämien, insbesondere die günstigen Erfolge bei der nur die Milz betreffenden Form der lymphatischen Leukämie, Strahlentherapie **56**:526, 1936.

288. Meyer, O. O.; Middleton, W. S., and Thewlis, E. W.: Therapeutic Failure with Certain Organic Substances in Leukemia, Folia haemat. **53**:166, 1935.

nodes, beef duodenum, hog spleen and beef bone marrow by mouth or after the administration of extracts of the last three substances parenterally.

O'Brien [211] studied the effects of roentgen therapy on the leukemias. Fifty per cent of the patients with lymphatic leukemia did not live longer than three and three-tenths months after therapy was begun. The average duration of life after roentgen therapy was fourteen and six-tenths months. In chronic myelogenous leukemia it was twenty-one and nine-tenths months. There was no convincing evidence that irradiation prolonged life, as some patients had a slow type whereas others had a more fulminating type of the disease.

INFECTIOUS MONONUCLEOSIS

Although not generally recognized, infectious mononucleosis has been known as a disease entity since 1885, when Filatow described the disease as an idiopathic lymphadenopathy. A similar disease occurring in children was observed by Pfeiffer in 1889 and termed by him glandular fever. The importance of the glandular involvement was stressed by Desplats in 1894. In the same year Horschelmann emphasized the appearance of a scarlatina-like eruption during the course of the disease. Sprunt and Evans in 1920 and Longcope in 1922 established the disease on a more secure clinical basis and termed it infectious lymphocytosis and infectious mononucleosis, respectively.

Dalley [289] and Poole and Findlay [290] reviewed the literature and adequately described the essential features concerning the etiology, pathology and clinical course of this disease. Various organisms have been isolated and described as the etiologic factor of infectious mononucleosis, but none of them has ever been confirmed by any except the original investigators. Usually the disease occurs in either sex at any age, although it is much more common in children and in persons under 40 years of age. There are three types with various clinical features and differences in the length of the prodromal periods. In the glandular type the prodromal period is from one to four days, and in the angiose type, from one to three weeks. The average period of incubation is seven or eight days.

The more common symptoms observed are headache, general malaise, sore throat, tenderness of the lymph nodes, backache, chilliness, anorexia, coryza, sweating, weakness, cough, dizziness, soreness and bleeding of the gums, nausea, stiff neck, epistaxis, stomatitis, abdominal pain, rash, photophobia and conjunctivitis. The physical signs usually encoun-

289. Dalley, G.: An Attack of Glandular Fever, St. Barth. Hosp. J. **43**:98, 1936.

290. Poole, L. T., and Findlay, H. T.: Laboratory Diagnosis of Glandular Fever (Infectious Mononucleosis), J. Roy. Army M. Corps **66**:145, 1936.

tered are fever, enlargement and tenderness of the nodes, injection of the throat, enlargement of the spleen, enlargement of the tonsils, membranous angina and a maculopapular rash.

The complications which may be encountered are variable. Dalley stated that the most usual ones are sepsis, hemorrhages, hematuria, purpura, conjunctivitis, jaundice, appendicitis, meningismus and involvement of the respiratory tract.

An elevated white blood cell count of varying degree is encountered at some time during the course of the illness; leukopenia may occur at the onset. The red blood cell count and the hemoglobin content are within normal limits. The exact classification of the atypical mononuclear cells observed is difficult, and although most authors are of the opinion that the cells are of the lymphocytic group, there are many opponents of this view. Freeman [291] reported 2 cases of typical infectious mononucleosis and gave observations on the bone marrow. He stated that the marrow spaces are filled with the typical cells (immature lymphocytes) which are present in the peripheral blood.

Downey and Stasney [292] described a fairly characteristic picture in nodes which were removed for biopsy during various periods of the acute illness. Grossly the nodes are of variable size, soft and spongy, with a distended white capsule. At the height of the disease there is extreme hyperplasia of the lymphoid tissue and the reticulum. There is a dense aggregation of atypical basophilic lymphocytes, which suggests early leukemia, but there is never complete obliteration of the structure of the node, nor is there any invasion of the capsule. In the advanced stages the germ centers and follicles have disappeared. The irregularity of the hyperplasia of the reticulum and lymphoid tissue gives the node a characteristic nodular and spotty appearance. Transitional stages between normal and atypical lymphocytes have been observed. The cells present in the nodes are the same as those described in the bone marrow and peripheral blood. In the author's opinion many of the atypical characteristics of the lymphocytes may develop after these cells enter the circulating blood. Downey and Stasney concluded that the histologic and cytologic pictures are suggestive of a leukemoid reaction to an infectious toxic lymphotropic agent which is present in the lymph nodes.

The prognosis is good, though relapses and remissions are not uncommon. Apparently the disease is self-limiting. The course may be protracted, and both glandular and hematopoietic changes may persist for many months. The diagnosis can usually be based on the presence of the painful nodes and the characteristic changes in the

291. Freeman, W.: Bone Marrow Studies in Glandular Fever (Infectious Mononucleosis), Am. J. Clin. Path. **6**:185, 1936.

292. Downey, H., and Stasney, J.: The Pathology of the Lymph Nodes in Infectious Mononucleosis, Folia haemat. **54**:417, 1936.

blood. Poole and Findlay substantiated the specificity of the heterophilic antibody test, which was originally described by Paul and Bunnell. Stuart, Griffin, Fulton and Anderson [293] also confirmed the value of this test, but in their opinion the antibodies are not of the Forssman type, as was previously suggested by other investigators.

AGRANULOCYTOSIS

Interest in agranulocytosis during the past year has continued to center about the rôle of certain drugs as etiologic factors in the causation of the disease. The theory that aminopyrine may be responsible for the disease in certain susceptible persons has received fairly widespread acceptance. It is known, however, that many persons may take large amounts of the drug without producing the syndrome. Nor is it the sole etiologic agent, as other drugs, such as dinitrophenol, apparently have been responsible for its production in some instances.

Another point of interest in regard to the condition is our impression that the incidence of the disease is decreasing, although there is no definite evidence that the sale to the public of aminopyrine alone or in combination with other drugs is decreasing.

Although all observers are not in accord, Rawls [294] claimed that sufficient data have been accumulated to indicate that aminopyrine bears some causal relationship to agranulocytosis. He administered over 100,000 tablets of aminopyrine or aminopyrine mixed with magnesium carbonate to 400 patients in clinic or in private practice. In 4 (1 per cent) of these patients agranulocytosis developed, and 3 died of it. Exclusive of the 4 patients, there were no significant changes in the white blood cell count or polymorphonuclear neutrophil percentages of 100 patients who received a mean daily dose of about 13 grains (0.85 Gm.) for a mean interval of approximately eighty-four days. It is considered that aminopyrine does not produce hematologic changes except in isolated cases, in which there probably is an idiosyncrasy to it.

Nammack and Thorsteinson [295] studied the blood of 100 patients with various diseases, chiefly rheumatism and infections of the upper respiratory tract, who were treated with a combination of salicylic acid and antipyrine. Antipyrine contains a benzene ring and is closely related in chemical structure to aminopyrine. Repeated examinations of the

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293. Stuart, C. A.; Griffin, A. M.; Fulton, M., and Anderson, E. G. E.: Nature of the Antibodies for Sheep-Cells in Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **34**:209 (March) 1936.

294. Rawls, W. B.: The Effect of Amidopyrin upon the Red, White and Polymorphonuclear Blood Cells of a Series of One Hundred Patients, Am. J. M. Sc. **192**:175, 1936.

295. Nammack, C. H., and Thorsteinson, N.: Study of One Hundred Cases with Administration of Drug (Salipyrine) Containing Benzene Ring, New York State J. Med. **36**:803 (May 15) 1936.

blood of the patients did not show a significant change in the total white blood cell count or in the percentage of neutrophils, nor was there any change of importance in the Schilling count. From a review of the literature and their own experience the authors concluded that neutropenia in connection with drugs containing the benzene ring probably depends on individual idiosyncrasy to this type of drug.

Witts [296] said that the evidence incriminating aminopyrine as the chief cause of agranulocytic angina may be classified as circumstantial, experimental and direct. He mentioned that in England the "Poisons List Confirmation Order", which went into force on May 1, 1936, makes it necessary to have a written order before aminopyrine can be supplied.

Parker and Kracke,[297] in attempting to produce the disease experimentally, caused leukopenia (usually less than 1,000 leukocytes per cubic millimeter) in rabbits by the subcutaneous injection of benzene in olive oil and showed that these animals had a marked depletion of the biologically active or reduced glutathione in the bone marrow and the blood. They suggested that a depletion of this form of glutathione in human blood and bone marrow may lead to various leukopenic states.

Benjamin and Biederman [298] reported observations on the blood of a subject after the oral administration of 10 grains (0.6 Gm.) of novaldin (sodium phenyldimethylpyrazolon methylaminomethane sulfonate), a drug which is closely related to aminopyrine. This preparation was given to a woman aged 50, who previously had had several attacks of agranulocytosis after the ingestion of aminopyrine. Eight hours after the drug was given subjective symptoms appeared (chilliness and fatigue, followed by slight fever, headache and backache). Within twenty-four hours the white blood cell count had fallen from 5,300 to 2,800 per cubic millimeter, and the polymorphonuclear neutrophil cells had been reduced from 72 to 46 per cent. Intracutaneous, patch and passive transfer tests with novaldin gave negative results. The authors concluded that this drug may produce the same deleterious effects as aminopyrine on the hematopoietic system.

This view has been substantiated by Klumpp,[299] who reported the case of a patient in whom agranulocytosis developed after the use of

296. Witts, L. J.: (*a*) Prophylaxis and Treatment of Agranulocytosis, Brit. M. J. **1**:1061 (May 23) 1936; (*b*) Effect of Toxic Substance on Blood-Forming Organs, with Special Reference to Therapeutic Drugs, ibid. **2**:211 (Aug. 1) 1936.

297. Parker, F. P., and Kracke, R. R.: Further Studies in Experimental Granulopenia, with Particular Reference to Sulphydryl (Glutathione) Metabolism in Blood Dyscrasias, Am. J. Clin. Path. **6**:41, 1936.

298. Benjamin, J. E., and Biederman, J. B.: Agranulocytic Leukopenia Induced by a Drug Related to Aminopyrine, J. A. M. A. **107**:493 (Aug. 15) 1936.

299. Klumpp, T. G.: Agranulocytosis Associated with the Administration of "Novaldin," a Derivative of Aminopyrine, J. A. M. A. **108**:637 (Feb. 20) 1937.

this drug for headache. The patient succumbed after a fulminating illness of six days, during which time he had the characteristic symptoms of agranulocytosis. Examination of the blood showed: red blood cells, 5,000,000; hemoglobin, 90 per cent, and white blood cells, 150, per cubic millimeter. Examination of the smear showed only 20 leukocytes, and 18 of these were lymphocytes and 2 were monocytes. There was no response to treatment with liver extract, pentnucleotide and blood transfusions. Pathologic examination showed, in addition to an acute necrotizing process in the mouth and throat, hypoplasia of the bone marrow.

Goldman and Haber [300] reviewed the literature concerning the relation between dinitrophenol and granulopenia and added the report of an additional case which they observed. Their patient, a girl of 13 years, had taken 0.1 Gm. of the drug daily for forty-six days. At the end of this time she had lost 25 pounds (11.5 Kg.). The following symptoms then appeared: weakness, malaise, feverishness, sore throat and vomiting. Examination showed the patient to be acutely ill and irrational. The throat was deeply injected, and a purulent exudate was present on the tonsils and uvula. The submaxillary glands were palpable and tender. The temperature was 105.6 F., the pulse rate, 136, and the respiratory rate, 32 per minute. Examination of the blood showed: hemoglobin, 88 per cent; red blood cells, 4,600,000; white blood cells, 700; lymphocytes, 100 per cent, and platelets, 180,000. The Derrien test of the urine for dinitrophenol gave positive results. A direct smear of the throat showed gram-positive cocci, and culture yielded Streptococcus viridans of the alpha type. Death resulted after a rapid, fulminating course of a few days, despite the administration of liver extract intravenously and intramuscularly, a blood transfusion, the use of the oxygen tent and finally tracheotomy. Autopsy failed to reveal any changes in the granulopoietic system. The authors stated that their case is the fourth one to be reported which could be attributed to dinitrophenol. The three other patients recovered after withdrawal of the drug and the use of such measures as pentnucleotide, roentgen therapy, blood transfusions, injections of leukocytic cream and various supportive measures.

The bone marrow of 24 patients who died of agranulocytic angina was studied by Darling, Parker and Jackson.[301] They divided the subjects into three groups, as follows: those who died within four days of the clinical onset of the condition, those who died from five to ten days after the beginning of their illness and those in whom death occurred after an illness of more than ten days. The changes found were so uniform in the bone marrow that the authors considered the

300. Goldman, A., and Haber, M.: Acute Complete Granulopenia with Death Due to Dinitrophenol Poisoning, J. A. M. A. **107**:2115 (Dec. 26) 1936.

301. Darling, R. C.; Parker, F., Jr., and Jackson, H., Jr.: Pathological Changes in the Bone Marrow in Agranulocytosis, Am. J. Path. **12**:1, 1936.

condition a disease entity. The patients with rapidly fatal agranulocytic angina showed lack of maturation in the granular series and hyperplasia of the stem cells. Those who had had a longer illness usually showed hypoplasia of the myeloid tissue, with the coincidental appearance of many plasma cells and lymphocytes. The recovery stage is described as characterized by rapid development of the stem cells into melocytes, metamyelocytes and polymorphonuclear neutrophil cells. These changes, in the authors' opinion, substantiate the previous contention of other investigators that the condition in the bone marrow is one of arrested maturation.

There have been no striking contributions to the treatment of agranulocytosis during the past year. Perhaps the most important therapeutic measure is the avoidance of aminopyrine and closely allied drugs in the treatment of patients with agranulocytosis or those who have previously had the disease. Murphy [302] considered that sufficient evidence is not available to establish the intramuscular use of liver extract as the treatment of choice in agranulocytic angina but suggested that further experience may demonstrate that this preparation is as valuable in the control of this disease as it is in pernicious anemia. In Witts' [290a] opinion pentnucleotide, transfusions, liver extract, arsphenamine and roentgen treatment are not specific therapeutic agents.

BONE MARROW

The study of bone marrow is becoming more routine as to the differential diagnosis of blood dyscrasias. With only a few standards of "normal," the present material serves best as supplying data for the future evaluation of biopsy and autopsy material.

Jaffé [303] summarized certain features of the study of marrow and described the condition in persons with normal marrow and in those with anemia, polycythaemia vera, agranulocytosis, leukemia, thrombocytopenia purpura, hemophilia or tumor of the bone marrow.

Higgins and Stasney [304] found that after splenectomy in rats there was marked stimulation of the red blood cell-forming tissue, which reached its peak the second week after operation. This was accompanied with anemia. There was a contemporary depression of leukocyte-forming elements.

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302. Murphy, W. P.: Progress in the Treatment of Some Diseases of the Blood, Minnesota Med. **19**:73, 1936.

303. Jaffé, R. H.: The Bone Marrow, J. A. M. A. **107**:124 (July 11) 1936.

304. Higgins, G. M., and Stasney, J.: Changes in the Bone Marrow and Peripheral Blood Following Splenectomy in White Rats: Preliminary Report, Proc. Staff Meet., Mayo Clin. **11**:446 (July 8) 1936; Folia haemat. **56**:189, 1936.

Osgood and Muscovitz [305] and Osgood and Brownlee [306] have developed a method for allowing the survival and multiplication of bone marrow cells in vitro.

An extensive study of bone marrow has been published by Segerdahl.[307] The conditions in various diseases have been described by numerous authors. Wainright and Duff [308] have reported quantitative studies of the marrow of the femur and vertebrae in monocytic leukemia. Suárez [309] has studied the sternal bone marrow of normal persons and of persons affected with uncinariasis, sprue, Banti's disease and Schistosomum Mansoni, comparing the numbers of cells with those of venous blood. Carnot, Lavergne and Mallarmé [310] found the study of bone marrow useful in the differential diagnosis of leukemia and myeloma. Tötterman [81] and Löwinger [82] have reported details of the marrow in hemolytic jaundice. Jones [311] gave the results of biopsies of bone marrow of patients with pernicious anemia during a relapse. Heilbrun,[131] using the section method, studied the marrow of a patient with macrocytic anemia of pregnancy. Darling, Parker and Jackson [301] presented the findings in agranulocytosis. Rosenthal and Grace [312] noted the changes due to radium poisoning in rabbits. Tecilazic [313] studied the conditions in normal infants.

Details of the technic of obtaining bone marrow have been given by Karavanov,[314] van der Merwe [315] and others. Van der Merwe used

305. Osgood, E. E., and Muscovitz, A. N.: Culture of Human Bone Marrow: Preliminary Report, J. A. M. A. **106**:1888 (May 30) 1936.

306. Osgood, E. E., and Brownlee, I. E.: Culture of Human Bone Marrow: A Simple Method for Multiple Cultures, J. A. M. A. **107**:123 (July 11) 1936.

307. Segerdahl, E.: Ueber Sternalpunktionen, Acta med. Scandinav., supp. 64, 1935, p. 1.

308. Wainright, C. W., and Duff, G. L.: Monocytic Leukemia, Bull. Johns Hopkins Hosp. **58**:267, 1936.

309. Suárez, R. M.: Comparative Study of Sternal Marrow Aspirated During Life and Venous Blood (Preliminary Report), Bol. Asoc. méd. de Puerto Rico **28**:87, 1936.

310. Carnot, P.; Lavergne, H., and Mallarmé: A propos de la myélographie chez l'adulte, Compt. rend. Soc. de biol. **121**:314, 1936.

311. Jones, O. P.: Cytologic Studies of Biopsied Pernicious Anemia Bone Marrow During Relapse, Proc. Soc. Exper. Biol. & Med. **34**:694, 1936.

312. Rosenthal, M., and Grace, E. J.: Experimental Radium Poisoning: Bone Marrow and Lymph-Node Changes in Rabbits, Produced by Oral Administration of Radium Sulphate, Am. J. M. Sc. **191**:607, 1936.

313. Tecilazic, F.: Ricerche ematologiche "in vivo" sul midollo osseo nella prima infanzia: Il midollo osseo nel lattante in condizioni normali, Pediatria **43**: 1046, 1935.

314. Karavanov, G.: A propos de la technique de la ponction de la moelle osseuse pendant la vie, Sang **10**:562, 1936.

315. van der Merwe, C. F.: Bone Marrow Studies in the Clinic, Folia haemat. **55**:108 and 218, 1936.

the puncture aspiration method, somewhat like that of Osgood. He reported data on the marrow of persons with pernicious anemia, carcinoma of the stomach, chlorosis, steatorrhea, familial hemolytic jaundice, infectious mononucleosis, syphilis and aplastic anemia.

Huggins, Blocksom and Noonan [316] and Huggins and Blocksom [317] found that fatty marrow of rats could be transformed into actively hematopoietic tissue by raising the temperature. Studies were made of the marrow of the rabbit, the pigeon and the albino rat.

HEMATOLOGIC TECHNIC

It is doubtful that during the past year any real advances have been developed in the technic of examination of the blood. Numerous modifications of existing methods have been proposed, but for the most part their merits remain to be impartially demonstrated. In any laboratory certain refinements of procedure or apparatus will be found peculiarly adapted to local conditions.

Although not strictly a matter of technic, accumulated data relative to normal values find a natural place in the consideration of methods of hematologic examination. Such data have been compiled by Andresen and Mugrage; [318] Belk, Curtis and Wilson; [319] Fiddes and Whitney, [320] and Bethell. [127] Quantitative observations on the blood lend themselves especially well to statistical analysis and interpretation. The standard deviations and coefficients of variation of erythrocyte counts made on identical blood samples by mechanical means and by eye were calculated by Magath, Berkson and Hurn. [321] By Fisher's methods of analysis

316. Huggins, C. B.; Blocksom, B. H., Jr., and Noonan, W. J.: Experiments on the Distribution of Red Bone Marrow, J. A. M. A. **106**:325 (Jan. 25) 1936; Temperature Conditions in the Bone Marrow of Rabbits, Pigeon, and Albino Rat, Am. J. Physiol. **115**:395, 1936.

317. Huggins, C. B., and Blocksom, B. H., Jr.: Changes in Outlying Bone Marrow Accompanying Local Increase of Temperature Within Physiological Limits, J. Exper. Med. **64**:253, 1936.

318. Andresen, M. I., and Mugrage, E. R.: Red Blood Cell Values for Normal Men and Women, Arch. Int. Med. **58**:136 (July) 1936. Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, Am. J. Dis. Child. **51**:775 (April) 1936.

319. Belk, W. P.; Curtis, E., and Wilson, M. K.: Erythrocyte Counts, Hemoglobin, and Erythrocyte Volume in Normal Young Men and Women Residing in the Eastern United States, Am. J. Clin. Path. **6**:487, 1936.

320. Fiddes, J., and Witney, C.: Erythrocyte Count and Haemoglobin Percentage in the Blood of Adult Males in Saskatchewan, Canad. M. A. J. **35**:654, 1936.

321. Magath, T. B.; Berkson, J., and Hurn, M.: Error of Determination of Erythrocyte Count, Am. J. Clin. Path. **6**:568, 1936.

of variance Rosahn and Casey [322] found statistically significant differences in the blood formulas of 5 healthy men and of 6 healthy rabbits. They concluded that each individual possesses a characteristic blood picture, largely determined by genetic factors, and that a formula normal for one subject may signify abnormality in the case of another.

A modification of the congo red method of estimating plasma and total blood volume has been described by Olloz.[323] By the use of a photometer and a special injection technic, the quantity of dye injected can be reduced to 3.5 cc. of a 1 per cent solution, thus permitting frequently repeated determinations. Hedenius [324] has devised an apparatus for measuring the coagulation time by the observation of a transparent bead moving in a tube containing blood. The motion of the bead stops as soon as coagulation begins. Sharp and Schleicher [325] reported their results obtained with Bock's erythrocytometer in the measurement of the diameters of red blood cells and concluded that this method, based on halometry, gives approximately the same values for the mean diameter of erythrocytes as those obtained with the Echelon ocular micrometer, with the advantage of being much less time consuming.

As an incentive to the display of inventiveness the enumeration and classification of platelets is rivaled only by the attractions of the sedimentation rate. A modification of Rahdenburg's method of counting platelets has been devised by Danilin,[326] a diluent, a 3 per cent solution of sodium citrate, thirty-eight parts, and 1 per cent malachite green, one part, being used. For the count a red blood cell pipet is employed, and the platelets and erythrocytes are enumerated successively in the counting chamber. Leslie and Sanford [327] described a method of quantitative and qualitative estimation of platelets in their own plasma, depending on a consideration of the coagulation times of whole plasma, platelet-free plasma and platelet-rich plasma. Olef [328] continued his investigations of platelets and differentiated them into four groups

322. Rosahn, P. D., and Casey, A. E.: Quantitative Variations in Hemacytologic Constitution of Healthy Men and Rabbits, Am. J. M. Sc. **192**:456, 1936.

323. Olloz, M.: Zur Methodik der wiederholten Blutmengenbestimmung, Deutsches Arch. f. klin. Med. **178**:647, 1936.

324. Hedenius, P.: Apparatus for Determining Coagulation Time of Blood, Acta med. Scandinav. **88**:440, 1936.

325. Sharp, E. A., and Schleicher, E. M.: Bock's Erythrocytometer and Technic for Its Use, J. Lab. & Clin. Med. **21**:975, 1936.

326 Danilin, J. J.: Eine neue Methode der Thrombocytenzählung, Folia haemat. **55**:82, 1936.

327. Leslie, E. I., and Sanford, H. N.: Method of Quantitative and Qualitative Estimation of Platelets in Their Own Plasma, J. Lab. & Clin. Med. **21**: 1078, 1936.

328. Olef, I.: Differential Platelet Count: Its Clinical Significance, Arch. Int. Med. **57**:1163 (June) 1936.

according to size. He found in cases of thrombocytosis and in some conditions associated with thrombopenia an absolute or relative increase in the number of small platelets, considered juvenile, which possess high agglutinating properties. Incidentally, Olef's technic of enumerating platelets, an indirect method employing a fresh wet preparation of diluted blood, has in our experience proved eminently satisfactory as regards both accuracy and convenience.

New methods of determining the sedimentation rate of erythrocytes have been described by various investigators. Brooks [329] devised a tube fitted to a venipuncture needle with a stopcock near the end of the needle. In this way, blood enters directly the calibrated tube, which is previously moistened with a solution of potassium oxalate. Smith [330] developed a technic for the use of capillary blood that is especially adapted to determinations for infants and children but similar in principle to the macromethods in general use. A relatively simple photographic apparatus for the automatic and continuous recording of the sedimentation rate is described by Lee.[331] He called it a sedimentometer. Sasano, Ordway and Medlar [332] studied certain extrinsic factors which may influence the sedimentation rate. Of these, temperature was most important, and they recommended that the test be made as a routine in an incubator at 37.5 C. Changes in barometric pressure produced slight but relatively insignificant differences. Manipulation of the blood should be reduced to a minimum, because of its effect on the suspension stability. Several anticoagulants were tested, and results closely agreeing with those secured with heparin were obtained by the use of a 1.1 per cent solution of potassium or sodium oxalate, one part of anticoagulant solution to three parts of blood. Capillary blood may be used, and a formula is provided for correction of the rate according to the volume of packed cells. A general review of the subject of the sedimentation test, including a detailed exposition of his own method, has been published by Wintrobe.[333]

329. Brooks, C.: New Method and New Pipette for Blood Sedimentation, J. Lab. & Clin. Med. **21**:971, 1936.

330. Smith, C. H.: Method for Determining Sedimentation Rate and Red Cell Volume in Infants and Children with Use of Capillary Blood, Am. J. M. Sc. **192**:73, 1936.

331. Lee, T.: Sedimentometer: Photographic Apparatus for Automatic Recording of Blood Sedimentation Rate, Brit. M. J. **2**:809 (Oct. 24) 1936.

332. Sasano, K. T.; Ordway, W. H., and Medlar, E. M.: Study of Certain Factors Which Influence Sedimentation Rates of Erythrocytes with Especial Emphasis upon Effect of Temperature, Am. J. Clin. Path. **6**:432, 1936.

333. Wintrobe, M. M.: Erythrocyte Sedimentation Test, Internat. Clin. **2**:34, 1936.

Book Reviews

Diseases of the Air and Food Passages of Foreign-Body Origin. By Chevalier Jackson, M.D., and Chevalier L. Jackson, M.D. Price, $12.50. Pp. 994, with 2,000 illustrations, including 3 plates in colors. Philadelphia: W. B. Saunders Company, 1936.

This book is divided into two parts. The first part is 333 pages long and is in reality a textbook of diseases of foreign body origin. The second part is 636 pages long and tabulates the kinds of foreign bodies which the Jacksons have removed in 3,266 instances from the air or food passages of their patients, the location of each foreign body, the type of operative procedure carried out in its removal and the result of treatment in each case.

To a medical layman unfamiliar with the authors' methods the volume as a whole is as exciting as a mystery story. The chapters in the first part of the book are delightfully written and are full of practical details regarding the etiology, the symptoms and the physical signs of foreign body deposits in the air or food passages. About half the textbook deals with such matters. The other half deals with treatment and describes bronchoscopy, esophagoscopy and the manner in which foreign bodies can be removed from the air or food passages.

The second part of the volume is equally engrossing. It is composed of a series of tables, and with each table is a photograph of the foreign body described. There is a short summary giving the patient's age; the nature of the foreign body; the anesthetic used in its removal; the problem presented, for instance, whether the safety pin in the larynx was open, pointed upward or embedded or whether the false teeth in the esophagus required version before they could be extracted; the result of the operative procedure, and the time required in its performance.

A book of this scope and character is bound to be extremely useful. Medical men will find it good reading for what it has to say from the point of view of the diagnosis of the various conditions it describes. All surgeons interested in bronchoscopy or esophagoscopy will wish to read it, and those who actually are concerned with the removal of foreign bodies from the air or food passages will find it an indispensable vade mecum.

Clinical Heart Disease. By Samuel A. Levine, M.D. Price, $5.50. Pp. 445, with 97 illustrations. Philadelphia: W. B. Saunders Company, 1936.

The author of a textbook of medicine should be able to write clearly and concisely, should have something to teach and considerable experience in teaching it and should have a comprehensive experience covering the whole field about which he writes. While embodying in his book the consensus of the best medical practice, he should not hesitate to state advanced ideas that have not yet received general acceptance but which have stood critical, practical tests in his own experience.

Dr. Levine has met these qualifications and has achieved this end in his textbook. He writes in a conversational style, as though standing at the beside of a patient and discussing the manifold aspects of a specific cardiac lesion. However, this facile style is a little misleading, and it is easy for the reader to overlook some important points.

The author announces his intention of writing a textbook for the general practitioner and then actually accomplishes this amazing feat. No complicated system of classification or references are included. The discussion of each type of cardiac disease includes sound advice as to treatment. Careful perusal of the discussion of the correct interpretation of a systolic murmur should lessen the tendency to make a diagnosis of valvular lesion without justification and conversely should reduce the likelihood of failure to recognize a significant systolic murmur.

The chapter on electrocardiography is clearly written and contains much of practical importance, but it is doubtful if the general practitioner will be able to use this technical information to any great extent.

Altogether Dr. Levine's textbook will be of great value to the general practitioner, as well as to the physician who attempts to qualify as a specialist in the treatment of cardiac disease.

Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen. By D. Scherf. Third edition. Price, 6.90 marks. Pp. 290, with 10 illustrations. Vienna: Julius Springer, 1936.

The favorable reports given the previous editions of this volume may well be carried over to the third edition. The title has been changed to include the section on diseases of the blood vessels, which has been added to the text.

The discussion of peripheral vascular disease is brief, in keeping with the general trend of the book. Methods of investigation are first enumerated, such as observations on the temperature of the skin, oscillometry, the reactive test for hyperemia, tests of the reaction to histamine and roentgenographic visualization of vessels. A brief but lucid description of the essential features of each disease is then given.

In the domain of cardiac disease itself, several new sections add completeness to the survey of the subject. Congenital heart disease, pericarditis and bacterial endocarditis are considered. A section on the important types of arrhythmia has been added and rectifies a conspicuous omission in former editions. Extrasystoles, auricular fibrillation and the tachycardias, particularly paroxysmal tachycardia, receive the major consideration.

The general tone of the book remains unchanged. All additions, in keeping with the older material, are brief but well written.

Cushny's Pharmacology and Therapeutics. Eleventh edition. Revised by C. W. Edmunds, M.D., and J. A. Gunn, M.D., D.Sc. Price, $6.50. Pp. 808, with 70 illustrations. Philadelphia: Lea & Febiger, 1936.

The reviewer, in a general way, disapproves of attempts to perpetuate a book by publishing revisions after the original author is dead. Often it seems as though the motive of the publisher is to retain the advertising value of a great name and that the man who revises the book could probably write a better text of his own. This criticism hardly applies, however, in the present instance, since from the nature of the subject any alteration from the original will be more in the way of additions than revisions. For example, the facts stated by Professor Cushny about morphine are probably as true today as they were at the time the first edition was published, and the task of bringing the book up to date is mainly one of describing agents which have been newly developed. One does not have the problem of a complete change of point of view, such as obtains in a clinical subject. It is a pleasure, therefore, to the reviewer to see again a new edition of this old friend in much the same format as the volume he labored over in student days.

The Study of the History of Science. By George Sarton. Price, $1.50. Pp. 75, with 6 illustrations. Cambridge: Harvard University Press, 1936.

Nowadays in the program of medical education increasing emphasis is being placed on the history of medicine. Students, who heretofore were taught nothing of the lore of the medical guild, now often become first class amateur historians and, occasionally, are trained as professional historians by those schools fortunate enough to have a department of medical history.

Here is a booklet to delight the heart of any one with a historical bent. It sketches in barest outline what the study of the history of science means, how such a study is conducted and whither such a study may lead. It is charmingly written. It is the sort of volume that should be on the open shelves of every medical library as a particularly tempting morsel of bait to be gobbled up by hungry-minded students.

A Textbook of Surgery. By John Homans, M.D. Fourth edition. Price, $8. Pp. 1,267, with 530 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

The difficulty in the past with textbooks of surgery has been that too much stress has been laid on operative technic, which is of little value to the medical student, who must learn technic in the laboratory and the operating room. Dr. Homans recognizes all this and frankly emphasizes diagnosis and general principles of therapy rather than controversial points on whether to cut and suture here or there. The book, nicely published, well illustrated and entertainingly written, appeals to the reviewer as by far the most useful textbook of surgery he has seen for the medical student.

Techniques chirurgicales. By A. Gosset. Price, 125 francs. Pp. 434, with 219 illustrations. Paris: Masson et Cie, 1936.

Professor Gosset and a group of his associates at the surgical clinic of the Salpêtrière have collaborated in preparing this publication, which includes a description of the important construction details and equipment incorporated in the new clinic building, an outline of the organization and functions of the laboratories, a chapter on sterilization of surgical supplies, a chapter on anesthesia and several chapters on surgical subjects selected at random. The chapters on surgical subjects include general observations and reveal the management, especially the surgical procedures, applied at the Salpêtrière in selected types of cases.

Differentialdiagnose in der inneren Medizin. By Prof. Dr. Med. O. Naegeli. Price, 9.60 marks. Pp. 414, with 42 charts. Leipzig: Georg Thieme, 1936.

This volume is one section of a larger work on differential diagnosis in internal medicine. One naturally has respect for anything written by Professor Naegeli, but the reviewer doubts the value of dealing with differential diagnosis as an isolated subject, and this feeling is supported in the present instance. It seems that the matter herein contained would be more useful if presented in connection with a complete discussion of the various diseases.

Arbeit und Gesundheit. Edited by Martineck. **Number 28: Kreislaufkrankheiten und Nierenkrankheiten bei Kriegsbeschädigten Häufigkeit, Erscheinungsform und Verlauf.** By Dr. Ludwig Delius. Price, 4 marks. Pp. 125, with 8 tables and 17 charts. Leipzig: Georg Thieme, 1936.

This little volume deals with follow-up studies of patients who acquired nephritis or cardiac disease during the war. The chief conclusion is that the nephritis ran the usual course of Bright's disease, 50 or 60 per cent of the patients recovering completely and the remainder showing chronic changes.

Die Sternalpunktion als diagnostische Methode. By Hans Schulten, M.D. Price, 18 marks. Pp. 82, with 16 plates. Leipzig: Georg Thieme, 1937.

This book gives an admirable discussion of the histologic picture of bone marrow. The technic of obtaining material by sternal puncture is taken up in detail, and there are many excellent plates of marrow cells in various diseases.

News and Comment

AMERICAN HEART ASSOCIATION, INC.

The Thirteenth Scientific Session of the American Heart Association will be held on June 7 and 8, 1937, from 9:30 a. m. to 5:30 p. m., in the Viking Room, Hotel Haddon Hall, Atlantic City, N. J. On Monday, June 7, the program of the Section for the Study of the Peripheral Circulation will be given. The general program will be presented on Tuesday, June 8.

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